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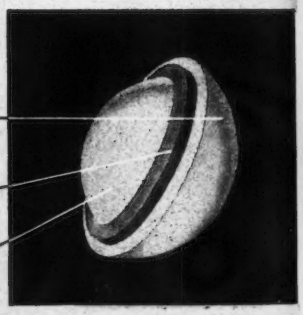

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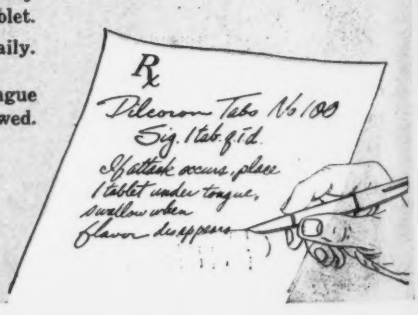

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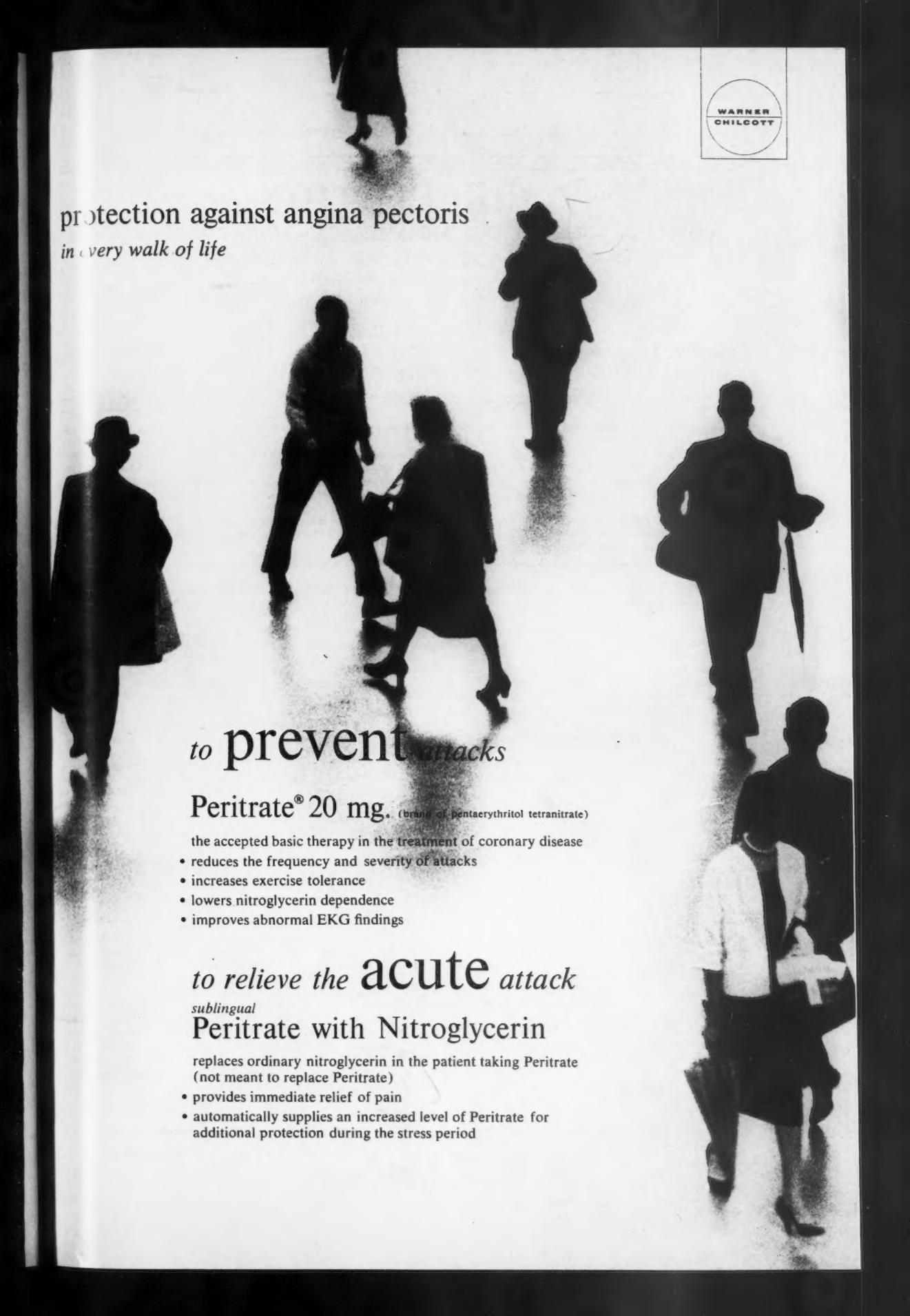
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Editorial

Tenfold in Ten Years

TEN years ago the American Heart Association, while remaining a scientific society, became a voluntary health agency which undertook research as its distinctive and major aim. The importance given this function is shown in the stipulation that *not less than* half of the dollars reaching the National Office must go to the *direct* support of research, while remaining funds provide for all other functions, including costs of administering the Association's research program. A Research Committee of investigators representing various disciplines bearing on cardiovascular disease was commissioned with the development and administration of this program. Thus the Committee had its first meeting in January of 1949. Members of this, the "Founder's Group," were: Dr. Tinsley R. Harrison, President, Dr. Howard B. Burchell, Dr. Louis N. Katz, Dr. Ann C. Kuttner, Dr. Myron Prinzmetal, Dr. Howard B. Sprague, Dr. Eugene A. Stead, Jr., Dr. Lewis Thomas, Dr. Francis C. Wood, Dr. Harland G. Wood, Dr. Harry Goldblatt, and Dr. Robert Bayley. Dr. Louis N. Katz was elected Chairman.

The Research Committee had a dual function: it was to be responsible for recommendations on research policy as well as for allocation of funds.* Succeeding committees have retained these responsibilities adhering for the most part to the basic policies established by the Founder's Group. One such theme has been emphasis on the productive research person rather than on the nature of his project. This concept was implemented in the Fellowship, Established, and Career Investigatorship programs. Grants-in-Aid were made from funds left after meeting meritorious requests for personal support.* Another policy was that a proportion of all funds—once indicated as not less than a tenth—be set aside for support of basic research in fields of inquiry not obviously related to cardiovascular disease. Such support has always been more than 10 per cent and currently engages more than 30 per cent of the research funds.

The Committee has done little detailed forward planning since its early days. Other forms of research support—student and predoctoral fellowships, traineeships, "block" grants to distinguished investigators, groups or institutions for periods up to 5 years, and large and long-term commitments needed for major studies in the epidemiology and prevention of diseases and in rehabilitation—have been periodically discussed, but without definite action. Funds available were never enough to meet existing programs and it was

*Until last year, questions of policy were periodically re-examined by the Committee to Review Research Policy.

*The secondary status of the grant program was implicit in the former practice of limiting Grants-in-Aid to amounts of no more than $10,000 annually and to periods of no more than 2 years. This practice distributed a relatively small sum in such a way as to bring stimulation and modest help to a fairly large number of investigators, thus serving to keep the Committee in contact with laboratories to which the Association's contribution was not large.

considered that the experience of several years was needed for their proper evaluation. Confidence in the Fellowship program was strengthened in 1955 by a survey that showed it was having the desired effect of orienting a large proportion of former Fellows into careers in investigation. Belief in the effectiveness of this form of research support grew as members of the Committee gained increased personal knowledge of the Fellows and the Investigators, of their work and of their stature among their colleagues.

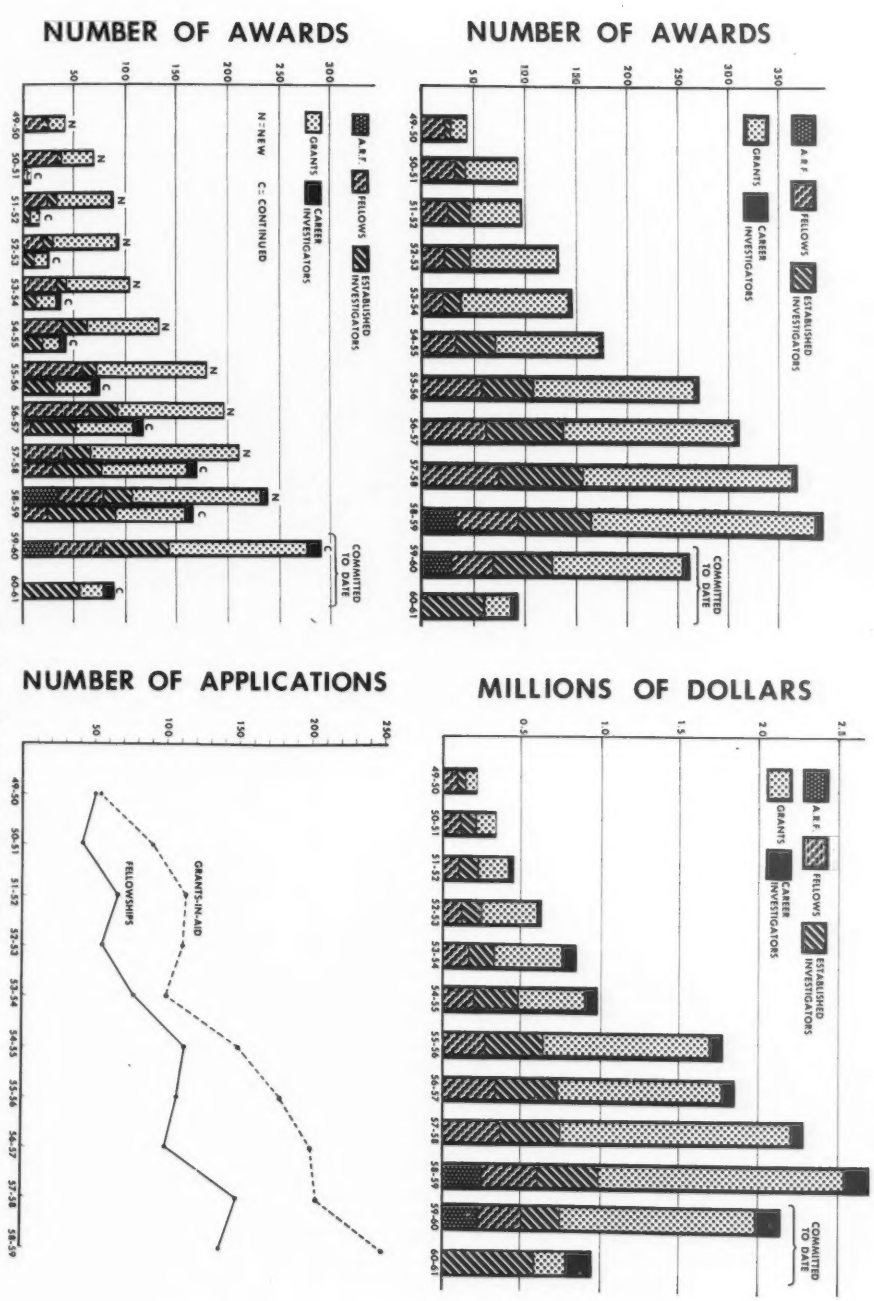
Meanwhile the burden on the Committee had become very great, as can be seen from data in the accompanying charts. The first Research Committee had available $225,000 and received 57 Fellowship and 60 Grant-in-Aid applications. It recommended 31 Fellowships and 6 Grants-in-Aid. This year (1957-1958) the Committee was responsible for $2,500,000, of which $1,350,000 was already committed; it had to consider 133 applications for Fellowships in all categories and 256 for Grants-in-Aid. Because the Association's Finance Committee added $500,000 of accumulated reserve to the $1,150,000 available, the Committee was able to recommend 82 new Fellowships, 20 new Established and 3 new Career Investigatorships, and 158 new Grants-in-Aid. Unfortunately, most of these last could only be given partial support, averaging about two thirds of the sums requested. Even this painful and dubious expedient failed to provide more than moral support for 36 projects which the Committee had recommended in principle.

Several factors have contributed to this shortage of funds. One, initiated in 1955, was provision of larger grants for longer periods than before, having in mind the increased costs and the need for continuity in research. Next, confidence in the Established Investigators was reflected in the decision in 1957 to review their applications for Grants-in-Aid at the same time as their applications for the Investigatorships; this was done to avoid consideration of overlapping requests, to help the Investigators expedite their research programs, and also to increase their identification with the Association by undertaking a larger part of their research support. In 1957, the Committee, recognizing a status intermediate between that of the beginner in research and the Established Investigator, established the class of the Advanced Fellow,* and in 1958 instituted allowances for dependents of Advanced Fellows and Investigators.

These changes in procedure, each of them costly, were directed primarily toward making the research function more effective, with some incidental hope of decreasing the paper work of investigators and of the Committee. However, there was no concurrent detailed scrutiny of future finance, since in previous years the supply of funds had fairly well kept pace with the volume of applications. The result was that the 1957-1958 Grant-in-Aid program was only rescued from near ineffectiveness by drawing on a reserve that will not be available again. Further, members of the Committee do not believe that scientists should continue to be given substantially less than they justify in their budgets. To maintain the orderly growth of its program, the Committee therefore will require one to one and a half million dollars which its does not have for the 1959-1960 program, the larger figure representing full support of potentially recommendable awards.

Officers of the Association and members of the Research Committee have made urgent appeals to Affiliates and Chapters to undertake full or partial support of appointments and awards recommended by the Committee. The response (over $50,000 as of July 1) is encouraging, but so far, it is inadequate. Perhaps the appeal was made too late in the year for Affiliates and Chapters to change their plans in such a way as to undertake large new commitments. But the problem remains and

*The Committee believes that Affiliates and Chapters should begin now to establish or augment fellowship programs for beginning individuals in research; the applications of these can be more rapidly and as fairly reviewed at the local as at the national level. It has also recommended that the Councils of the Association undertake greater responsibility in the review of applications for Grants-in-Aid.



FIRST-DECADE GROWTH OF AMERICAN HEART ASSOCIATION RESEARCH PROGRAM

Top, left, Number of awards in various categories, by years. *Top, right,* Dollars awarded, by years. *Bottom, left,* New (N) versus continuing (C) awards, by years. *Bottom, right,* Increase in number of applications, by years. Fellowships include Investigatorships.

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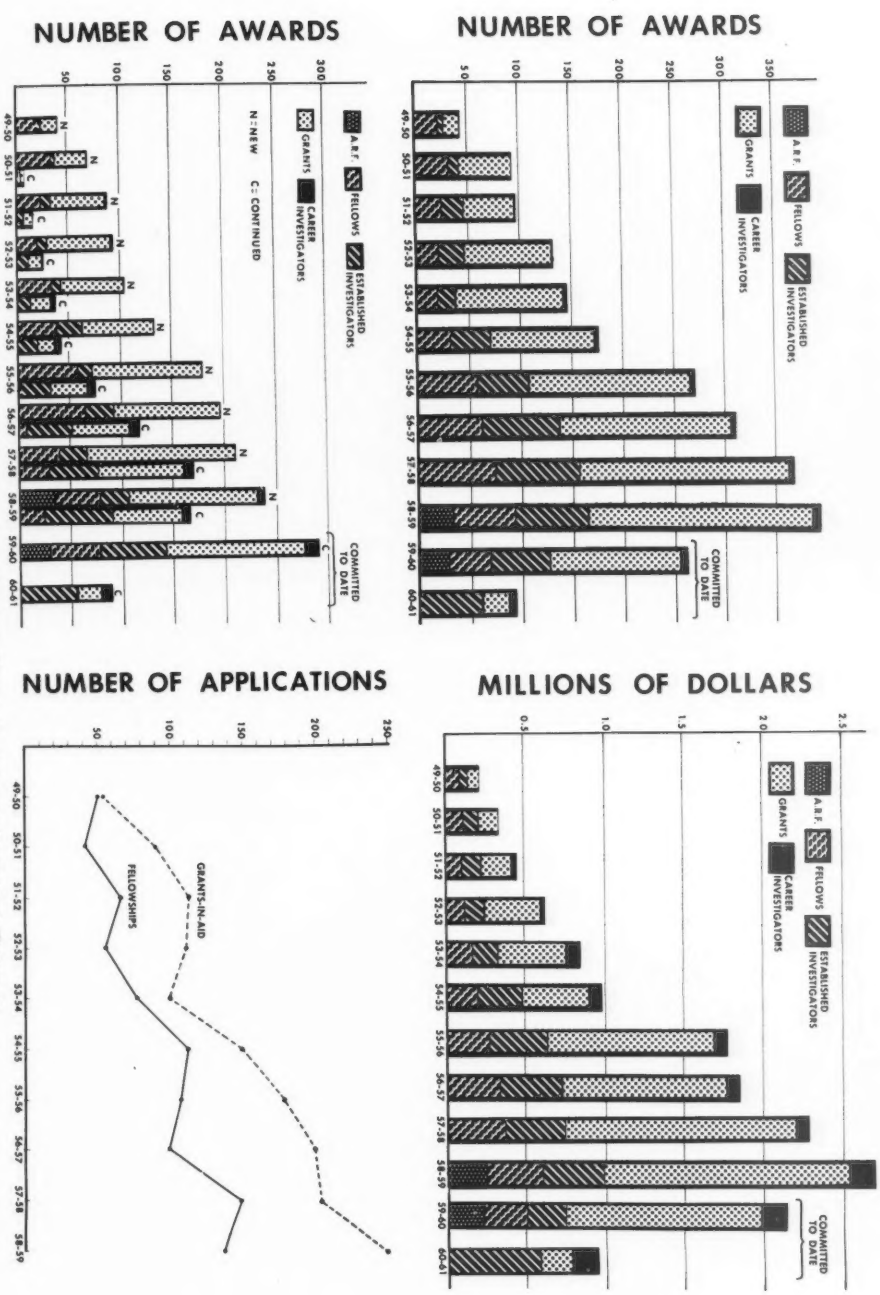

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must be examined further if it is to be solved.

Those who give dollars or dimes to a heart association give primarily because they are interested in research. Most people know that research is not regional. Its only boundary is truth and its only aim is the well-being of all of those who need the benefits of its accomplishment. The Research Committee's realization of this is shown by the fact that its awards—based on merit and on availability of funds—are geographically distributed through the United States in direct and constant proportion to the numbers and amounts of requests from the various parts of this country. The Committee provides regional support in proportion to apparent regional need. It is therefore an equitable and effective agent in the distribution of heart research funds wherever they may originate.

The Research Committee has been charged by the Assembly with the responsibility of reexamining the Association's research policies and the relation of these to those of Affiliates and Chapters and of other agencies making grants in the cardiovascular field. The result of this study will be presented to the Assembly for discussion and for formulation of plans for the years ahead. But plans, however well devised, cannot of themselves support an investigation. The urgent and present need is for increased financial support of the recommendations of the Committee.

One suggested procedure is that the Association seek funds for research from other agencies, corporations and institutions. It is not clear that this would accord with the basic philosophy of a voluntary health agency. Another suggestion is that the present 75 25 formula of fund allocation as between Affiliates and the National Office be revised, with an increased allocation of heart dollars to research at the national level. There may be other possibilities. Hence we present the problem for the consideration of all members of the American Heart Association, and of those administering research awards made by the Association. Our hope is that the deliberations of the forthcoming Assembly may thus develop a prompt and vigorous solution of the problem of research support at every level of the Association.

A. C. Corcoran
Chairman of the Research Committee
John H. Peters
Assistant Medical Director for Research

Lipid Keratopathy and Atheroma

By DAVID G. COGAN, M.D., AND TOICHIRO KUWABARA, M.D.

Lipid plaques in corneas of patients with lipid keratopathy, in corneas of hypercholesteremic rabbits and in the arteries of man and the hypercholesteremic rabbit are described. An interesting and thought-provoking analogy is drawn between the plaques that can be seen and followed in the eye during life with the more occult plaques of blood vessels in atheromatosis.

THE purpose of the present paper is to point out certain similarities in fatty plaques of the cornea and of blood vessels, both in man and in hypercholesteremic rabbits, and to suggest a common pathogenesis. The following résumé is based on a clinicopathologic study of approximately a dozen cases of lipid plaques in the human cornea, approximately the same number in the rabbit cornea, and a pathologic study of atheromata in man and in the experimental animal.*

The fatty plaque in the human cornea is of a specific type and comprises a separate entity. It develops, often precipitously, in or adjacent to an area of abnormal vascularity. The fat may appear during the stage of neovasculogenesis in association with an active keratitis, or it may develop in an otherwise white and quiet eye, years after the keratitis. In the former case the fat is apt to assume a fan-shaped distribution in advance of the vascular arcade, while in the latter case it is likely to be disk-shaped and situated in the immediate area of the blood vessels (figs. 1 and 2). Moreover it is usually reversible when it occurs in a swollen cornea, that is, during an active keratitis, whereas it is usually permanent and stationary when it occurs in a compact cornea. Although associated with abnormal vascularity, the development of the fatty plaque is not necessarily associated with reactivation of the initial inflammatory process (it is often interpreted as a dystrophy) and its only symptom other than a cosmetic one is reduced vision.

While the foregoing description is that of a typical case, variants are common. Thus, when the fat forms in a cornea that has been diffusely vascularized, there will be a correspondingly diffuse inundation with fat, instead of the plaque-like distribution that is characteristic of localized vascularity. Another variant is that in which the fat is deposited in a cornea having a conspicuous arcus senilis (fig. 3). It is then difficult to tell where the arcus ceases and the new deposit of lipid begins.

It is not always possible to determine from the literature whether the foregoing entity or something else is being described. However, instances of it have probably been described under the following clinical headings: fatty dystrophy of the cornea,[1] dystrophia adiposa corneae,[2-4] adiposis of the eye,[5, 6] xanthomatosis,[2, 7, 8] lipin interstitial keratitis,[9] lipidosis corneae,[10] and secondary steatosis.[11] The multitude of names indicates the diversity of interpretations that have been attributed to the process. We shall call it simply lipid keratopathy, realizing that this does not adequately distinguish it from other fatty changes in the cornea, such as arcus senilis or true fatty dystrophies, if such exist.

Several observers have suggested a relation of this lipid keratopathy to hypercholesteremia[8, 12, 13] or to generalized xanthomatosis,[14]

From the Howe Laboratory of Ophthalmology, Harvard University Medical School, Massachusetts Eye and Ear Infirmary, Boston, Mass.

This work was aided by grants from the Greater Boston Chapter of the Massachusetts Heart Association and the American Heart Association.

*Cholesterol was added to the rabbit chow, and feeding continued for periods of 6 to 12 months. Blood cholesterol levels reached 1 to 2 Gm. per 100 ml.

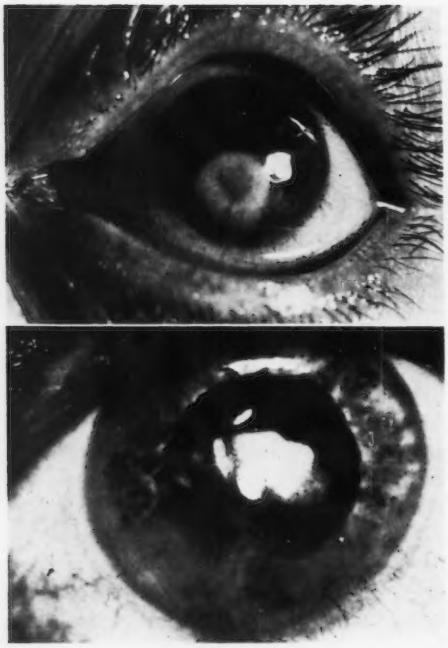

FIG. 1 *Top.* Lipid keratopathy forming a disk-shaped plaque, from a 48-year-old woman who had a corneal ulceration and considerable residual interstitial vascularization. Approximately 2 months after ulceration the dense opacity developed in all layers of stroma but most especially in deeper layers. No subsequent change noted over several months. Noteworthy was a blood cholesterol level of 500 mg. per cent and a fatty acid level of 627 mg. per cent.

FIG. 2 *Bottom.* Lipid keratopathy forming a fan-shaped plaque in advance of the vascular arcade in a 61-year-old man who had had a bullous keratopathy and selerokeratitis thought to be part of a rosacea keratitis. Considerable interstitial vascularization of the lower portion of the cornea. During neovascularization patient precipitously developed arcuate opacity (presumed fat) just in advance of vessels and separated from them by a clear zone (*light reflex superimposed*). With further ingrowth of vessels into swollen cornea, dense opacity disappeared, leaving only scintillating particles, presumed cholesterol.

FIG. 3. Diffuse lipid keratopathy in a patient who had had an interstitial keratitis as a child leaving residual vascularization. Recently cornea has become opaque. Extensive deposition of material, believed fat, having a ring-like distribution suggestive of an extensive arcus senilis. Other eye had less vascularization and only a mild arcus senilis.

and at least one observer has suggested a relation to atheromatosis.[15] We shall discuss this at some length.

Histologically, these fatty plaques of the cornea in man contain 2 types of sudanophilic lipid (fig. 4, *top*). First there are the bright red droplets, often as large as 20 μ in diameter, situated predominantly within the cells. These are abundant in proportion to the cellularity of the tissue. Secondly, there are the sudanophilic granules situated predominantly in the acellular and hyalinized areas. With low-power microscopy these give the impression of a diffuse sudanophilia. The former we shall call globular lipid and the latter granular lipid. These 2 types are not only separable on morphologic grounds but there is some mutual exclusiveness in their distribution in that one or the other tends to dominate one area. Thus the granular type of sudanophilia is usually sparse or absent from areas of globular sudanophilia. The reverse is not so true. Furthermore, the inescapable impression is that the granular lipid is derived from the globular lipid when the cells containing the latter disintegrate.

With hematoxylin and eosin stains, the cornea with lipid keratopathy shows an increase in cellularity in some areas and a decrease of cells or hyalinization in others. Some of the cells have a distended or vacuolated cytoplasm, but it is impossible to state whether they are distended corneal cells or invading macrophages. Often, when frozen section of the cornea are examined with polaroids, [illegible] re-

frin:ent crystals are abundant, especially in the areas of hyalinization (fig. 4, *middle and bottom*).

Fatty plaques similar to those in human beings may be induced in hypercholesteremic rabbits if their corneas are vascularized (fig. 5). If vascularization is induced before putting the animals on a high-cholesterol diet, lipid will be deposited to some extent in the paravascular regions, but if a localized vascularization is induced while the animal is hypercholesteremic a dense lipid plaque will develop in the area of blood vessels. The relationship between trauma and deposit of fat in the cornea was early pointed out by Versé and Rohrschneider[16] and its similarity to the lipid plaques of man has recently been emphasized by us.[17]

Histologically these plaques in hypercholesteremic rabbits consist of an abundant intracellular, globular, sudanophilic material, an increase in cellularity of the cornea, a variable amount of birefringent crystals, and a variable, but usually small, amount of extracellular, granular sudanophilic material (fig. 6). In other words, the induced plaques of hypercholesteremic rabbit corneas are similar to those in human corneas, except that there is less necrosis and correspondingly less granular sudanophilia in the rabbit.

Fatty plaques in human blood vessels have, of course, been abundantly described under the heading of atheromata. These plaques consist of focally thickened intima containing masses of sudanophilic and birefringent material (fig. 7). The sudanophilia consists, as in the case of lipid plaques of the human cornea, predominantly of intracellular globular lipid and extracellular granular lipid. The former is present and relatively abundant in regions of cellularity while the latter is present predominantly in regions of hyalinization and necrosis. Often there is a conspicuous mutual exclusiveness between the two, as was noted in the case of the cornea (fig. 8). The portion of the intima adjacent to the lumen and, to a less extent the portion adjacent to the media, tends to be cellular and to be rich in globular lipid, whereas that in the more intermediate zones tends to be relatively acellular and contains the granular type of lipid. This is consistent with the sugges-

FIG. 4 *Top.* Cross section of cornea from a patient with lipid keratopathy, cut in the frozen state and stained with hematoxylin and Sudan IV. Noteworthy is abundant sudanophilia presenting globular and granular form. The former is chiefly intracellular and present in areas of fibrocytosis; latter is entirely extracellular and present in areas of relative acellularity. *Middle.* Same case photographed between partially crossed polaroids to show birefringent crystals (*white areas*). *Bottom.* High-power magnification, same case, showing crystals as photographed between completely crossed polaroids.

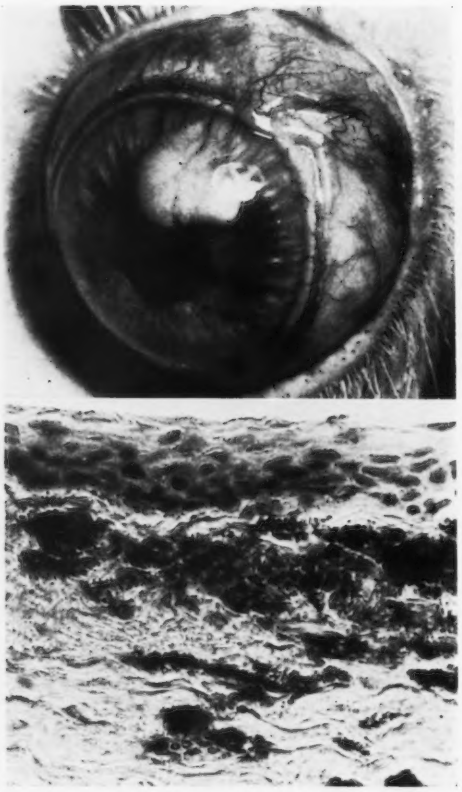

FIG. 5 *Top.* Lipid plaque in hypercholesteremic rabbit cornea occurring at site of vascularity. Cornea had been cauterized several times by heated probe.

FIG. 6 *Bottom.* Sections of rabbit cornea in region of plaque, stained with hematoxylin-Sudan. Noteworthy is abundance of intracellular globular lipid and relatively slight amount of granular sudanophilia.

tion that the granular sudanophilia is derived from the globular sudanophilia as the tissue becomes necrotic (fig. 9). The birefringent crystals also seem to precipitate out with necrosis, being absent from the fat-laden areas adjacent to the lumen but variably abundant in the necrotic intermediate layers.

The fatty plaques in the blood vessels of rabbits show changes that are practically identical with those of human atheromata. See figure 10. In both cases the plaques tend to localize about orifices of blood vessels, a fact that has been attributed to the intimal vascularity of these regions.[18] Elsewhere they also appear to be associated with vascularity of the intima.[19] The plaques consist of hyperplastic intima loaded with sudanophilic material and birefringent crystals. These have the same distribution as in human atheromata, that is, intracellular globular lipid adjacent to the lumen and media with extracellular granular lipid in the intermediate necrotic areas. In general, however, the necrosis is less marked in the case of the rabbit than of the human atheroma. The mutual exclusiveness of the 2 types of lipid referred to is often striking in the rabbit atheroma. The birefringent crystals, which in the aggregate may be massive, are associated predominantly with the areas of necrosis and can be seen by ordinary light microscopy.

DISCUSSION

The chief basis for identifying the fatty plaques of the cornea and those of blood vessels is the similarity in their histologic features. Common to both are the intracellular globular lipid and the extracellular granular lipid. The former is associated with active hyperplasia of tissue and the latter with hyalinization and necrosis of tissue. In both there tends to be a mutual exclusiveness of the 2 types, and one appears to be converted into the other with necrosis of the tissue, in the direction of globular to granular sudanophilia. Associated with this is a release of birefringent crystals that appear to be, in part at least, cholesterol.

There are differences, however small, in the fatty plaques of the corneas of man and of hypercholesteremic rabbits; necrosis is less marked in the latter and there is less calcification. These same differences apply to a comparison of atheroma of man and the hypercholesteremic rabbit, and have been attributed to the differences in the acuteness and duration of the process in the two. Time lapses of the plaques of man are measured in terms of decades, whereas those of rabbits are a matter of months. In any case, the plaques in the human cornea are more analogous to those of human atheromata, whereas the

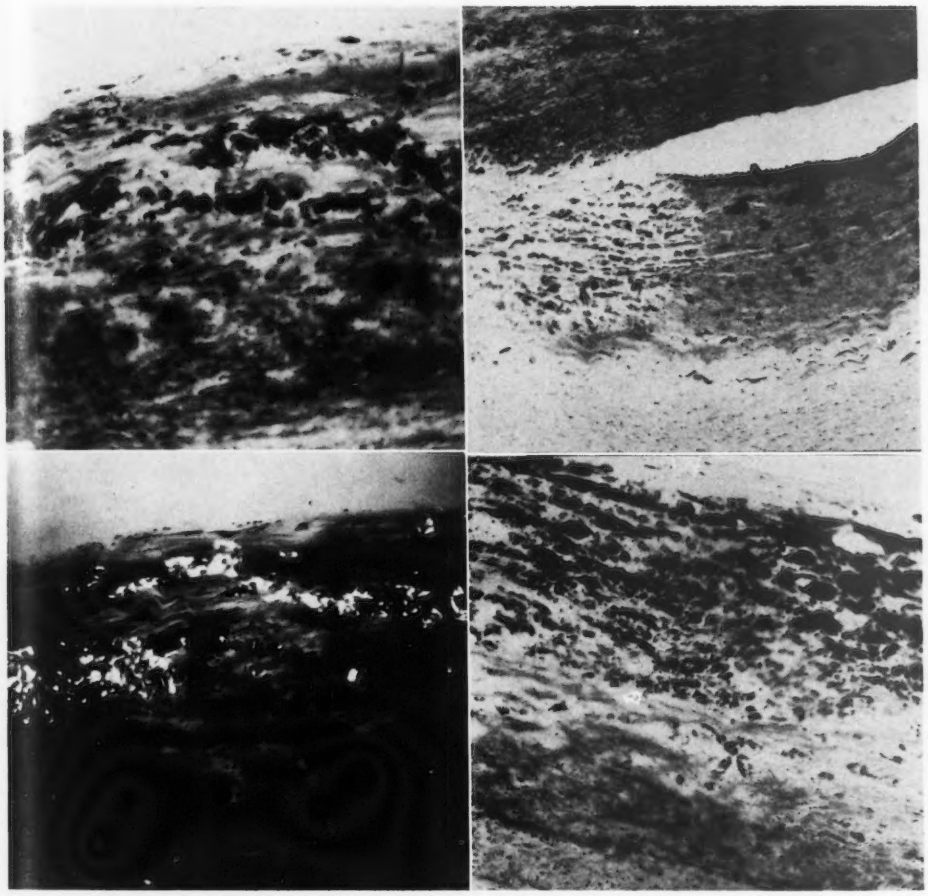

FIG. 7 *Left. Top.* Human atheroma (aorta) showing extensive granular sudanophilia and some extracellular globules of fat in relatively necrotic portion of the intima. Sections stained with hematoxylin-Sudan IV. *Bottom.* Same section examined between crossed polaroids. Birefringent crystals.

FIG. 8 *Top, right.* Human atheroma illustrating "mutual exclusiveness" of extracellular granular and intracellular globular lipid.

FIG. 9 *Bottom, right.* Human atheroma. Usual globular lipid within cells adjacent to lumen and granular lipid in necrotic deeper layers of intima.

plaques of the hypercholesteremic rabbit cornea are more strictly comparable to the atheromata of the rabbit blood vessels. In both cases however, what is happening in the cornea appears similar to what happens in the blood vessels of the corresponding species.

If the pathogenesis and course of events for the two are identical, as is suggested by the histologic findings, one would expect atheroma to develop only in areas of prior vascularization, and that with episodic suddenness. Both these possibilities have indeed been suggested on other grounds, but it has not heretofore been generally recognized that the cornea is an informative analog where the processes could be visualized during life.

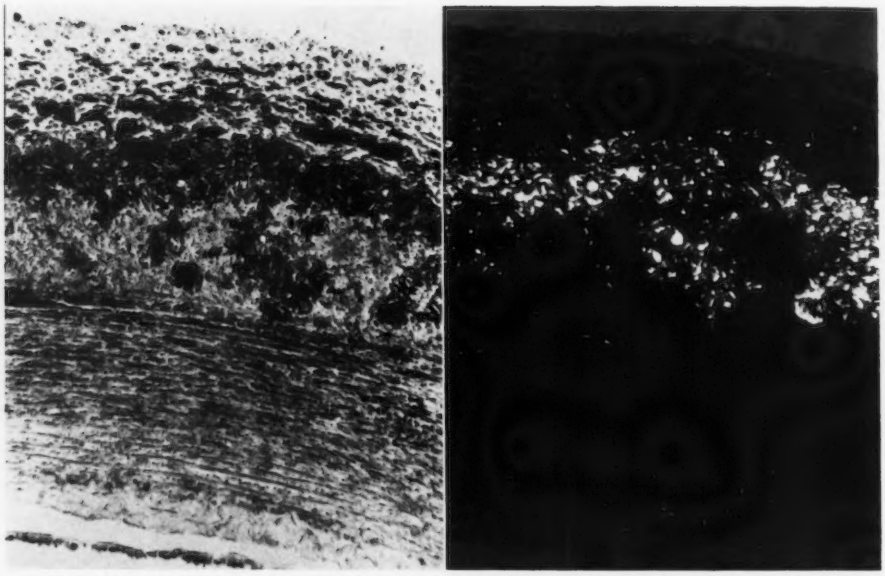

FIG. 10 *Left.* Rabbit atheroma (aorta) showing intracellular globular lipid adjacent to lumen and granular sudanophilia with cholesterol crystals in necrotic deeper layers. *Right.* Same section examined between crossed polaroids.

The possibility that patients with this type of lipid keratopathy are prone to atheromatosis or vice versa cannot be answered on the basis of the present cases, since no autopsies were done on the patients with corneal plaques. In any case it would be difficult to establish a significant correlation, since all persons in the age group of most of the patients in this study normally have atheromata. It would perhaps be more pertinent to enquire whether species that do not normally develop atheroma can develop lipid keratopathy. It is interesting, therefore, to note that one case has been reported of lipid keratopathy in the dog.[20]

It is also pertinent to enquire whether or not patients who develop lipid plaques in the cornea are those with hypercholesteremia. Of the 10 patients in this series who had one or more blood cholesterol determinations, the average level was 267 mg. per cent. In 4 of these the level was more than 300 mg. per cent and in 1 (fig. 1) the level was over 500 mg. per cent with a fatty acid level of 627 mg. per cent. The literature also records cases of lipid plaques in the cornea with elevated plasma cholesterol.[3] It thus appears that lipid plaques occur in the cornea, as they do in blood vessels, predominantly but not exclusively in patients with higher than average blood cholesterol levels.

Finally, it is probably worth pointing out that the analogy drawn between lipid keratopathy and atheroma no doubt has its counterpart in arcus senilis and diffuse sudanophilia of the intima. However, no comparable study of these has as yet been made, and we mention it only to avoid confusion with the entities represented by the present cases.

SUMMARY

Lipid keratopathy as described in the present paper consists clinically of a fatty plaque in an area of the cornea that has been previously vascularized. It often occurs with remarkable suddenness and may be stationary or reversible, depending on the condition of the cornea. In any case it is not necessarily associated with activation of the original inflammatory process.

A similar plaque may be induced in the hypercholesteremic rabbit by vascularizing the

cornea. This also consists of abundant fat in the region of vascularity.

These fatty plaques of the human and rabbit cornea are histologically similar to those of blood vessels with atheromatosis. They also consist predominantly of an intracellular globular sudanophilia and an extracellular granular sudanophilia. The latter develops along with birefringent crystals and appears to be a function of necrosis.

It is suggested that lipid plaques of the cornea occur in a manner similar to atheroma of blood vessels and therefore provide a convenient analog for the visualization of the atheromatous process during life.

Summario in Interlingua

Ceratopathia lipidic, secundo le description offerite in le presente articulo, consiste—in terminos clinic—de un placa grassiose in un area del cornea que esseva previemente vascularisate. Frequentemente illo occurre con subitaneitate remarcabile. Illo pote esser stationari o revertibile, in dependentia del condition del cornea. In omne caso, illo non es associate necessarimente con activation del processo inflammatori original.

Un simile genere de placa pote esser inducite in conilios hypercholesterolemic per le vascularisation del cornea. Iste genere de placa consiste etiam de un abundantia de grassia in le region del vascularitate.

Tal placas del cornea de conilios o humanos es histologicamente simile a illos del vasos sanguinee que es affecite de atheromatosis. Illos omnes consiste predominantemente de un sudanophilia globular intracellular e un sudanophilia granular extracellular. Iste ultime se disveloppa insimul con crystallos birefringente e pare esser un function de necrosis.

Es exprimite le opinion que placas lipidic del cornea occurre in un maniera simile a atheroma del vasos sanguinee e representa per consequente un analogo convenibile pro le visualisation del processo atheromatose durante le vita del subjecto.

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Constrictive Pericarditis: Serial Hemodynamic Studies with an Explanation for Reversible Congestive Phenomena

By TIMOTHY R. MURPHY, M.D., JULIUS M. MEYER, M.D., AND JULES CHASE, M.D.

A new explanation for certain instances of acute reversible congestive phenomena in constrictive pericarditis is offered on the basis of 6 patients studied clinically and by right heart catheterization. In 2 cases intermittent tamponade in the presence of a rigid pericardium accounted for the reversibility of the congestive state, as contrasted with 4 cases presenting the chronic progressive course of classical constrictive pericarditis. The diagnosis in the 6 cases was proved by surgery or autopsy.

THE clinical picture of constrictive pericarditis with pericardial thickening and calcification together with the relentless and progressive course of the disease is the subject of many excellent papers.[1-5] However, only a single report[4] has been found on the reversible aspects of the congestive phenomena in constrictive pericarditis.

This report presents 2 cases of constrictive pericarditis exhibiting reversible congestive findings secondary to superimposed cardiac tamponade. Serial hemodynamic studies in 4 other cases of classical constrictive pericarditis are discussed.

Material and Methods

Right heart catheterization[6] was performed on 6 patients under basal conditions with no premedication. Repeated catheterizations were carried out in 4 of the patients over 1- to 4-year periods. In 2 patients postoperative measurements could not be obtained.

Pressure measurements were obtained in the right atrium, right ventricle, pulmonary artery, and pulmonary wedge position during rest and exercise. Cardiac output in the resting state was determined by the direct Fick method, usually in duplicate. All duplicate determinations agreed within 10 per cent. The average is used in table 1.

The exercise consisted of simple leg raising at a rate of 30 per minute for 7 to 8 minutes with measurements of cardiac output during the last 3 minutes of this period.

Expired air was collected in the Collins gasometer of the Tissot type. Blood gases were measured according to the method of Van Slyke and Neill and expired air was analyzed by the Scholander micrometer apparatus.[8]

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Case Reports

Cases with Reversible Congestive Phenomena

Case 1, R.B. This 50-year-old white man was hospitalized for a herniorrhaphy in August 1951. A chest film revealed extensive calcification over the left ventricle. The patient had no cardiovascular complaints until September 4, 1951, when frequent cough and breathlessness on effort appeared. On October 8 the rapid onset of severe dyspnea, chest oppression, and facial edema necessitated hospitalization.

Three episodes of pneumonia had occurred during childhood and early adult life.

On physical examination there was mild facial edema, cyanosis of the lips and distended neck veins; the blood pressure was 120/80. The cardiac rate was regular at 90. The heart tones were muffled and there were no murmurs. Bilateral basilar rales and a left pleural friction rub were present. The latter disappeared the following day. The liver edge was felt 5 cm. below the costal margin. There was no peripheral edema. The electrocardiogram demonstrated a sinus rhythm, low QRS voltage, and T-wave inversion in the standard leads. A chest roentgenogram revealed pericardial calcification, left atrial enlargement, pleural thickening at both bases, and a normal transverse diameter unchanged from August 1951. Digitalization, low-salt diet, and mercurial diuretics were followed by a 10-pound weight loss and marked clinical improvement. The venous pressure on the third hospital day was 220 mm. of water. A pericardial friction rub persisting for 24 hours was heard on the ninth hospital day.

On October 25, 1951, digoxin was stopped. There was no weight gain, venous pressures were unchanged, liver enlargement persisted, and 1 episode of transient atrial fibrillation occurred. The patient at this time was asymptomatic except for

breathlessness on effort. The results of cardiac catheterization on November 11, 1951, are recorded in table 1. He was redigitalized preoperatively without change in weight or symptoms.

At surgery on November 20, a thick calcified pericardium was found. On incision of the pericardium a milky fluid under pressure escaped. The blood pressure immediately rose 20 mm. Hg. The pericardium was adherent to the epicardium only at the apex. The epicardium had a dull gray appearance and calcium plaques covered one third of the anterior surface and one half of the posterior aspect. The presence of tamponade, secondary to the accumulation of pericardial fluid, as a cause of the acute congestive phenomena was not appreciated prior to surgery.

Postoperatively the patient did very well, until on the tenth postoperative day a wound infection accompanied by sternal separation occurred. Repeated surgical attempts to immobilize the sternum were unsuccessful. He died 20 days postoperatively. At necropsy the valves were normal and the foramen ovale was closed. Neither the etiology nor pathogenesis of the pericardial inflammation and pre-existing constriction could be ascertained. Cultures of the pericardial fluid were negative. Microscopic examination of the pericardium demonstrated calcification, fibrous thickening, and perivascular lymphocytic infiltration.

Comment. Cardiac catheterization (table 1, R.B.) revealed a cardiac index of 2.36 L. per min. per M.^{2} and moderate elevation of the pulmonary wedge, right ventricular end-diastolic, and right atrial mean pressures. The pulmonary "wedge" pressure had the configuration usually associated with mitral stenosis, though the mitral valve was normal at autopsy. In this instance, the configuration was probably secondary to constriction of the left ventricle with the atrium contracting against an elevated left ventricular end-diastolic pressure.[2]

The presence of calcification confirmed the impression that the pericardial involvement was of some duration. The left atrial enlargement would suggest that a minor degree of constriction about the left ventricle had been present for some time, despite the absence of symptoms. The immediate increase in the blood pressure on incising the pericardium establishes tamponade as the cause of the sudden failure.

This case represented mild chronic pericardial constriction with sudden congestive symptoms occurring only after the development of an acute pericardial effusion where the pericardium was thick and could not expand.

Case 2, G.E. This 28-year-old white man had pneumonia at ages 3, 18, and 28. The second episode was apparently of viral etiology with a stormy course and electrocardiographic evidence of toxic myocarditis or pericarditis. The third episode of pneumonia occurred on June 28, 1953 (fig. 1). Sudden dyspnea, chest oppression, atrial flutter, and syncope led to hospitalization on July 8, 1953.

Physical examination revealed cyanosis, neck vein distension, blood pressure of 110/70, a grade I apical systolic murmur, and hepatosplenomegaly. Sinus rhythm was restored with digitalis and symptoms abated, but hepatosplenomegaly and the murmur persisted. The electrocardiogram showed low QRS voltage and isoelectric T waves in the standard leads. The patient was discharged on the tenth day. Right heart catheterization was performed on November 17, 1953 (table 1, G.E.), 1 month after cessation of digitalis.

Breathlessness on effort and palpitation with occasional syncope required rehospitalization in May 1954. There had been no change in the physical findings since his discharge in July 1953. Cardiac fluoroscopy and venous pressure were normal. The electrocardiogram showed normal QRS voltage, a P-R interval of 0.24 second with wide, notched P waves, and isoelectric T waves in the standard leads. One episode of atrial flutter occurred while in the hospital with conversion to sinus rhythm by digitalis. The skin tests for tuberculosis were positive. The patient was discharged on August 24, 1954, with a diagnosis of "myocarditis of unknown etiology."

He was readmitted in January 1956 with exertional dyspnea, syncope, and facial edema of 2 days' duration. The physical examination was unchanged with the exception of progressive hepatosplenomegaly. Cardiac fluoroscopy now demonstrated pericardial calcification, predominantly over the posterior and diaphragmatic aspect of the left ventricle. There were frequent episodes of supraventricular arrhythmias.

The venous pressure varied between 210 and 224 mm. of water. An injection of a mercurial diuretic resulted in a 10-pound weight loss and right heart catheterization 2 days later (table 1, G.E.) demonstrated a resting right atrial pressure of 6 mm. Hg. Digitalization with intravenous digoxin resulted in no significant change in intracardiac pressures or cardiac output over a 3-hour

period. After a regime without medication or salt restriction, the venous pressure was 192 mm. of water, responding to mercural diuresis with a fall to normal.

The sudden onset of congestive phenomena, the fluctuation of venous pressures and symptoms, together with minimal variation in heart size over a 3-year period, suggested the diagnosis of constrictive pericarditis with superimposed tamponade. This diagnosis was confirmed at surgery on April 17, 1956, when a dissection of the thickened pericardium over the right ventricle revealed a space 10 by 10 cm. containing fluid under pressure. The fluid had a calcium value of 1484 mg./100 ml. and the cultures were negative. The postoperative course was uneventful, the symptoms and physical findings returning to normal. All medications were discontinued in July and right heart catheterization was repeated in October, 1956 (table 1, G.E.).

Comment. The right heart catheterization in 1953 revealed a low cardiac index of 1.65 L. per min. per M.^{2} and a right ventricular end-diastolic pressure of 12 mm. Hg. In 1956 the cardiac index had risen to 2.33 L. per min. per M.^{2} and the right ventricular end-diastolic pressure had fallen to 9 mm. Hg, with marked increases on exercise. The configuration of the resting pressure curves in 1953 and 1956 were only suggestive of constrictive pericarditis. The exercise curves in 1956 showed the "typical constrictive pattern." The studies 6 months after operation revealed a relatively unchanged cardiac index from that immediately preoperatively, but resting and exercise pressures were normal.

The pneumonia at age 18 was quite severe and accompanied by electrocardiographic changes compatible with pericardial injury. The third episode of pneumonia in 1953 was associated with a definite increase in heart size (fig. 1), low voltage on the electrocardiogram, and marked symptoms, and presumably marked the onset of the pericardial effusion limited by a thickened pericardium. Roentgenograms showed fluctuation in heart size between 1953 and 1956, being largest at the time of pneumonia in 1953 and smallest just prior to surgery in 1956.

After the pneumonia in 1953 the patient was in ill health with episodes of atrial arrhythmia, progressive hepatosplenomegaly, and fluctuating venous and right heart pressures. These alterations in clinical status, venous and right heart pressures, and cardiac output indicate a reversible element. Myocardial insufficiency and changes in blood volume have been suggested as causes for this reversibility.[4] A more plausible explanation in this case is the fluctuation in the volume of fluid within a rigid pericardial sac.

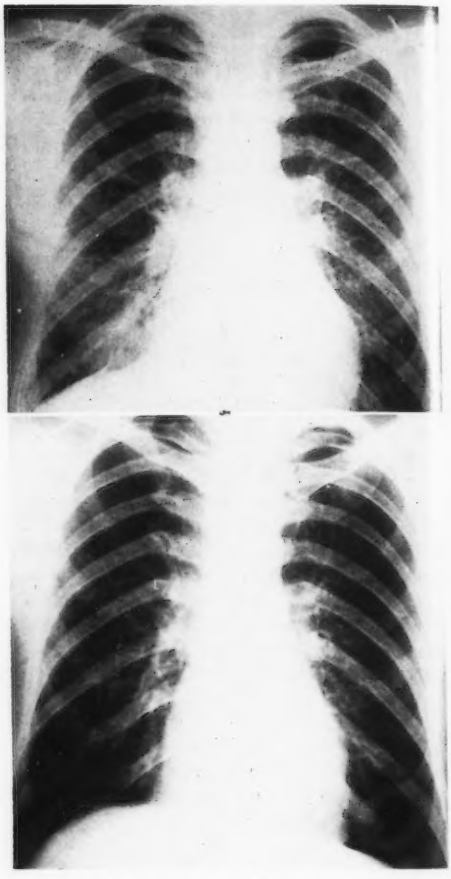

FIG. 1. *Top.* Patient G. E., June 29, 1953. *Bottom.* Patient G. E., April 11, 1956. Posteroanterior roentgenograms illustrating only the slight increase in heart size occurring with the right lower lobe pneumonia, although congestive failure was marked. The second film is prior to surgery and symptoms were minimal.

Postoperative right heart catheterization on October 18, 1956, 6 months after surgery, showed the intracardiac pressures to be within normal limits at rest and on exercise. The cardiac index had risen slightly.

Cases with Classical Features

Case 3, G.U. A 49-year-old white man was admitted in November 1941, with impending delirium tremens. The cardiovascular examination was negative except for distention of the neck veins. The electrocardiogram showed low voltage of the QRS-T complexes. No cardiac diagnosis was made and the patient was discharged after treatment for portal cirrhosis.

Subsequently, there were repeated hospital admissions with hepatomegaly appearing in 1942 followed 2 years later by ascites and exertional dyspnea.

In September 1951 the diagnosis of constrictive pericarditis was made and right heart catheterization was performed (table 1, G.U.). The patient refused surgery, and with salt restriction and mercurial diuretics was only moderately limited in his activity.

Pericardial calcification was first detected in 1953, at which time cardiac catheterization was repeated. The clinical status was unchanged.

In August 1954, an episode of atrial flutter responded to digitalis. The ascites, neck vein distention, peripheral edema, and exertional dyspnea became progressively more severe. Atrial fibrillation appeared in July 1955. Cardiac catheterization was repeated.

A few months later death occurred due to spontaneous thrombosis of the abdominal aorta. Autopsy revealed a constricting, heavily calcified pericardium with complete obliteration of the pericardial space. Portal cirrhosis was also present.

Comment. The major hemodynamic changes between the catheterizations of 1951 and 1953 included a definite fall in the cardiac index, unchanged right atrial pressures, and slight elevation of the right ventricular end-diastolic and pulmonary artery mean pressures (table 1).

The circulatory changes between 1953 and 1955 consisted of an unchanged cardiac index, despite the presence of atrial fibrillation, and a distinct rise in the right atrial and pulmonary wedge pressures.

The 35 per cent reduction in cardiac output between 1951 and 1953 was unaccompanied by discernible clinical deterioration. Progression of symptoms did not become manifest until 1 year later. Then clinical deterioration was relentless but the cardiac index showed no further fall.

Case 4, R.Ro. A 29-year-old white man was admitted June 21, 1953, with mild epigastric distress and occasional bouts of palpitation. The physical examination was negative. The diagnosis of duodenal ulcer was established and pericardial calcification was demonstrated by x-ray, the latter having been present since 1943. The electrocardiogram showed marked right axis deviation, vertical electric axis, and a left heart strain pattern.

Between 1953 and 1956 the only cardiac complaint was vague exertional fatigue. However, during this period, the patient was studied annually by right heart catheterization, which revealed progressive increases in right atrial, right ventricular end-diastolic, and pulmonary wedge pressures with no change in the cardiac output.

In view of the pressure increases, pericardectomy was performed in January 1956. A thick calcified pericardium was found with complete obliteration of the pericardial space. The patient returned to his road construction work in May 1956 and noted a distinct improvement in his work tolerance. In July 1956 right heart catheterization showed return of all pressures to normal at rest and during exercise, without change in the cardiac output.

Comment. Over the period of observation, the pressures increased without comparable progression of symptoms. This emphasizes that in chronic constrictive pericarditis appreciable pressure increases may occur with clinical manifestation so insidious that their significance is apparent only postoperatively.

Case 5, R.Ru. A 26-year-old white male musician was seen in October 1954, with progressive ankle edema, exertional breathlessness, and paroxysmal atrial flutter of 5 years' duration, considered to be secondary to rheumatic heart disease with mitral stenosis until pericardial calcification was detected in 1954. There were moderate cardiac enlargement, a grade II apical systolic murmur, neck vein distention, and hepatosplenomegaly.

Chest roentgenogram revealed extensive pericardial calcification with moderate enlargement of the left atrium and pulmonary artery, and minimal enlargement of the left ventricle. The electrocardiogram showed wide notched P waves, frequent atrial premature beats, and a left heart strain pattern.

TABLE 1.—*Hemodynamic Data in Six Patients with Constrictive Pericarditis*

Case and age (yr.)	Date of catheterization	State	Body surface area	Cardiac index (L./min./M.² BSA)	Oxygen consumption (ml./min./M.² BSA)	Respiratory quotient	A-V O_2 diff. (vol. %)	Pressure (mm.Hg)					Arterial blood oxygen	
								Right atrial mean	Right ventricle (s/d)	Pulmonary artery (s/d,m)	Pulmonary 'wedge' mean	Systemic artery pressure	cont. (vol. %)	sat (%
R.B.,* 50	11/9/51	R	1.9	2.36	148	.71	6.3	15	35/17	35/21,24	16	120/85	18.7	88
G.E., 30	11/17/53	R	2.00	1.65	122	—	7.3	10	25/12	25/10,—	—	110/70	—	—
	2/23/56†	R	2.00	2.33	126	.82	5.4	6	20/9	20/10,14	—	130/80	19.3	95
		E	—	—	—	—	—	16	40/20	44/20,30	—	—	—	—
	10/18/56†	R	2.02	2.56	134	.80	5.2	3	20/2	20/ 8,10	7	114/80	21.5	99
	(6 mo.postop.)	E	—	—	—	—	—	7	30/4	28/10,17	—	—	—	—
G.U.,* 59	12/8/51	R	1.94	2.61	119	.82	4.5	12	40/14	40/15,20	—	124/70	18.4	92
	11/24/53†	R	2.00	1.85	103	.85	5.7	12	40/17	40/22,25	16	110/80	18.7	95
	7/5/55†	R	1.86	1.75	116	.86	6.5	19	40/20	40/20,25	22	108/70	16.7	92
R.Ro., 29	8/25/53†	R	1.73	3.63	128	.78	4.0	4	28/2	28/10,14	—	128/88	17.6	93
		E	—	4.25	282	.85	6.7	15	31/17	31/15,28	11	—	17.7	91
	10/14/54	R	1.77	2.72	119	.89	4.4	11	30/15	30/10,18	—	140/96	17.3	91
		E	—	3.65	271	.84	7.4	16	38/18	38/16,23	—	—	17.9	97
	9/22/55†	R	1.76	2.75	133	.84	4.8	10	28/10	25/10,15	12	106/74	16.8	92
		E	—	3.84	368	1.03	9.6	17	42/17	42/25,30	22	—	17.9	98
	7/26/56†	R	1.80	2.69	120	.89	4.4	1	12/2	12/ 6,9	3	116/70	18.4	96
	(6 mo. postop.)	E	—	3.59	259	.90	7.2	2	14/2	14/ 7,10	10	—	18.8	97
R.Ru.,* 26	11/17/54	R	1.82	2.73	188	.86	6.9	26	45/25	40/30,35	28	140/80	21.5	95
H.T., 27	3/24/53	R	1.79	2.27	169	.86	7.5	13	36/18	35/20,25	—	110/74	18.2	100
		E	—	—	—	—	—	17	40/21	—	—	—	18.3	100
	11/16/54	R	1.80	3.05	159	.86	5.2	5	30/0	28/15,20	—	140/100	19.4	98
	(19 mo. postop.)	E	—	3.6	274	.92	7.6	13	—	27/12,22	—	—	18.9	92

* Postoperative catheterization not done.
† Done in duplicate, see text; R—Rest; E—Exercise.

Cardiac catheterization (table 1, R.Ru.) revealed a normal cardiac index, marked elevation of right atrial, right ventricular end-diastolic, and pulmonary wedge pressures.

Pericardectomy was performed in November 1954. A thick pericardium with obliteration of the pericardial space was found. Postoperative recovery was excellent.

Comment. Despite a 6-year period of severe symptoms and marked pressure elevation, this patient's cardiac output was within the normal range.

Case 6, H.T. A 27-year-old white man was admitted in November 1952 with melena and epigastric distress. The diagnosis of duodenal ulcer was established and pericardial calcification was demonstrated by x-ray, the latter having been present since 1948.

Cardiovascular complaints were elicited only on specific questioning and consisted of vague breathlessness on effort since September 1951.

Physical examination revealed dilated neck veins and moderate hepatomegaly. Cardiac examination was normal. The electrocardiogram showed nonspecific T-wave changes.

Right heart catheterization (table 1, H.T.) revealed a low cardiac index and moderate elevation of right atrial, right ventricular end-diastolic, and pulmonary artery pressures.

Pericardectomy was performed in April 1953. A thick calcified pericardium with obliteration of the pericardial space was found. Postoperative recovery was excellent. Right heart catheterization 19 months postoperatively revealed a normal cardiac index and normal pressures at rest with moderate elevation of the right atrial pressure during exercise.

Comment. This case illustrates that significant cardiac pressure elevations and reduced cardiac output may occur before the patient is aware of a limitation of activity.

Discussion

The congestive state in constrictive pericarditis is usually considered secondary to mechanical interference with ventricular diastolic filling resulting in reduction in stroke volume and cardiac output. Postmortem findings have also implicated myocardial atrophy[14] and hepatic and pulmonary phlebosclerosis[15] occurring after prolonged pericardial constriction. These mechanisms explain the slowly progressive course of constrictive pericarditis, but do not explain the sudden reversible episodes of congestion occasionally observed. Harvey and co-workers[4] implicated myocardial insufficiency and hypervolemia as causes of this reversibility.

An additional mechanism is illustrated by the findings at surgery in the cases R.B. and G.E. In these cases the formation of relatively small amounts of fluid within a rigid pericardial space with marked reduction in the diastolic volume would account for the rapid onset of congestive symptoms. With resorption of the fluid the patient may become asymptomatic. This fluid might be the result of an exacerbation of the original infection or a fresh pericardial insult. The presence of loculated fluid, limited by a rigid pericardium, has been described at surgery in other cases of constrictive pericarditis.[2, 9-11] However, the role of this fluid in production or the reversibility of the congestive state was not commented upon.

The remaining 4 cases had complete obliteration of the pericardial space, and presented the classical features of constrictive pericarditis. From our serial studies and reported hemodynamic studies of others,[1, 2, 5, 9] a pattern of the course of constrictive pericarditis may be constructed: 1. An initial phase of pericardial insult as a result of infection or trauma, may be followed in months or years by pericardial constriction (second phase). 2. Early in the second phase, the constriction is of such mild degree that intracardiac pressures are normal at rest, and elevated only with exercise (case 4, R.Ro.), As constriction progresses, intracardiac pressures rise until they are abnormal at rest. Symptoms may be absent or minimal although pressures are distinctly elevated, as demonstrated by venous pressures or cardiac catheterization (case 4, R.Ro., and case 6, H.T.). Similar cases have been described in other studies.[12, 13] 3. The third phase is one of obvious symptoms and usually occurs relatively late in the course of the disease. The pressures are regularly elevated but other factors must be active in the production of the congestive state, since similar pressures may exist in different patients with one relatively asymptomatic and the other moderately incapacitated. (case 6, H.T., case 3, G.U.) The duration of the cardiac constriction, as well as the severity, appears to play a role in the production of symptoms.

Summary

Hemodynamic studies were correlated with the clinical course of constrictive pericarditis in 6 patients. In 2 patients, with reversible congestive phenomena fluid accumulation and resorption in a rigid pericardial space is offered as an explanation for this reversibility.

The contrasting progressive course of classic, chronic, constrictive pericarditis is demonstrated in 4 patients.

The discrepancy between the symptoms and the height of intracardiac pressures is discussed.

ACKNOWLEDGMENT

The authors wish to acknowledge gratefully the assistance given them in the course of this investigation by Drs. Howard Correll and Ross C. Kory.

SUMMARIO IN INTERLINGUA

Studios hemodynamic esseva correlationate con le curso clinic de pericarditis constrictive in un serie de 6 patientes. In 2, le reversibilitate del phenomenos congestive es explicate per le resorption del fluido in un rigide spatio pericardial. Le 4 altere patientes monstrava per contrasto le curso progressive de classic constrictive pericarditis chronic.

Le discrepantia inter symptomas e nivello del pressiones intracardiac es discutite.

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Cheyne-Stokes Respiration. A form of respiratory distress, peculiar to this affection, consisting of a period of apparently perfect apnoea, succeeded by feeble and short inspirations, which gradually increase in strength and depth until the respiratory act is carried to the highest pitch of which it seems capable, when the respirations, pursuing a descending scale, regularly diminish until the commencement of another apnoeal period. During the height of the paroxysm the vesicular murmur becomes intensely puerile.—WILLIAM STOKES. *The Diseases of the Heart and the Aorta.* Dublin. 1854.

The Pathology of Hypertensive Pulmonary Vascular Disease

A Description of Six Grades of Structural Changes in the Pulmonary Arteries with Special Reference to Congenital Cardiac Septal Defects

By DONALD HEATH, M.D., AND JESSE E. EDWARDS, M.D.

Progressive histologic changes occur in the pulmonary arteries and arterioles, as a complication of chronically elevated pulmonary arterial blood pressure, in patients with congenital septal defects of the heart. This progression is so stereotyped as to allow a division of the structural effects into 6 grades. The histologic features of each grade are described in detail in this communication. These results afford a basis for comparing the magnitude of these changes to the clinical findings.

PROGRESSIVE histologic changes occur in the pulmonary arteries and arterioles, as a complication of chronically elevated pulmonary arterial blood pressure, in patients with congenital septal defects of the heart. The progression is so stereotyped as to allow a division of the structural effects into 6 grades (table 1), although it is recognized that there is a gradual change from one grade to another. This division is of great practical value, since it enables the pathologist to express a whole group of complex changes in a succinct manner as a grade number. In the present communication, based primarily on the study of 67 cases of congenital septal defects of the heart and 2 cases of idiopathic pulmonary hypertension, a detailed description is given of the histologic changes that characterize each grade. In 55 cases pulmonary hypertension was demonstrated at cardiac catheterization or at cardiotomy; in 9 instances elevated pressure in the pulmonary circulation was inferred from the clinical and pathologic findings. In the remaining 5 cases, the pulmonary artery mean blood pressure was less than 30 mm. of mercury; these were all cases of atrial septal defect studied to illustrate the grade-1 changes in this disease. No cases with pulmonary venous obstruction were studied although at least the earlier changes of hypertensive pulmonary vascular disease and pulmonary arteritis occur in this group of patients. In a companion paper,[1] the relation between each grade and pulmonary artery blood pressure, flow and resistance, and age is demonstrated. In a third study,[2] the relation between each grade and the reversibility of pulmonary hypertension after surgical correction of the cardiac anomaly is considered.

This paper is concerned solely with the changes found in small pulmonary vessels. Structural changes also are found in the intima and media of elastic pulmonary arteries. Atheroma is the characteristic intimal feature related to pulmonary hypertension in these large arteries. The configuration of the elastic tissue of the media of the pulmonary trunk differs in pulmonary hypertension that is acquired from that which is present from birth. These changes in the intima and the media and their relation to pulmonary hypertension are considered in detail elsewhere.[3, 4]

A description is given of the structural changes characteristic of each grade, as found specifically in cases of large ventricular sep-

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tal defect, large patent ductus arteriosus, or any other form of congenital heart disease associated with a free communication between the systemic and pulmonary circulations and pulmonary hypertension from birth. This qualification is necessary because the earliest changes seen in the pulmonary vessels in cases of atrial septal defect (or similar diseases associated with acquired pulmonary hypertension following a long period of high pulmonary blood flow) with increased pulmonary artery blood pressure are not identical with, although in some respects they are similar to, those seen in ventricular septal defect. Furthermore, in acquired idiopathic pulmonary hypertension, the early histologic changes associated with the elevation of blood pressure differ from those associated with ventricular septal defect. The histologic changes defined as grade 1 of hypertensive pulmonary vascular disease in the following section refer to changes seen in patients having congenital heart disease associated with pulmonary hypertension from birth. The corresponding grade of change seen in patients having atrial septal defect and acquired idiopathic pulmonary hypertension is dealt with at the end of the paper. It needs to be stressed, however, that, whereas grade-1 changes are simply an integral part of the various structural and functional alterations in large ventricular septal defect, structural changes of grades 2 and 6 occur as a result of the raised pulmonary artery blood pressure. Grades 2 to 6 are present among all forms of hypertensive pulmonary vascular disease, whatever the etiology, and are found in each of the 2 groups of heart disease referred to herein, as well as in idiopathic pulmonary hypertension.

Before the pathologic aspects of hypertensive pulmonary vascular disease are described, it is necessary to present the histologic features of normal pulmonary blood vessels.

Histologic Features of Normal Pulmonary Blood Vessels

The walls of the pulmonary arterioles consist of a single elastic lamina except proximally at their origin from a muscular artery where serial sections demonstrate their walls to consist of a thin media sandwiched between internal and external elastic laminae.[5] In the majority of patients beyond adolescence studied in this series and in groups of controls studied previously,[6] fine acellular intimal fibrosis was found in arterioles as a normal age change. As already stated, the vast majority of pulmonary arterioles do not have a muscular media beyond their immediate origin from a muscular pulmonary artery, but vessels as small as 80 μ in diameter with a thin but distinct muscular media, bounded by internal and external elastic laminae, can be found after careful search of sections of the normal lung.[7] These tiny vessels, which look like small muscular pulmonary arteries, are found predominantly in the lingula pulmonis.[8] Arterioles arise either as branches, at right angles to the parent stem, which is related to the respective alveolar duct, or as terminations, at an oblique angle, of small muscular pulmonary arteries. Branches of the former type also may arise from quite large muscular arteries near small bronchi and much more proximally in the pulmonary vascular tree than the arterioles that arise as terminations of muscular pulmonary arteries. They have a thin wall with a lumen-to-wall ratio of about 8:1.[5] Brenner[9] defined pulmonary arterioles as arterial vessels in the lung less than 100 μ in diameter, but obviously this is only an approximation. The main criteria employed in the recognition of arterioles apart from size are the structure of their walls and their origin from small muscular arteries.

The muscular pulmonary arteries, usually defined as arterial vessels between 100 and 1,000 μ in diameter,[9] consist of a thin media bounded by internal and external elastic laminae. The media is composed predominantly of smooth muscle with occasional collagenous and elastic fibrils. In small muscular arteries less than 300 μ in diameter the media has a thickness equivalent to 2.8 to 3.1 per cent of the external diameter of the vessel in the upper and lower lobes and 5.5 to 6.8 per cent in the region of the lingula. These figures have been confirmed previously by mensuration of medial thickness in this class

TABLE 1.—*Basis of Grades of Hypertensive Pulmonary Vascular Disease Found in Association with Large Ventricular Septal Defects and Functionally Related Diseases*

	Grade of hypertensive pulmonary vascular disease					
	1	2	3	4	5	6
Type of intimal reaction	None			Cellular		
				Fibrous and fibroelastic		
				"Plexiform lesion"		
State of media of arteries and arterioles			Hypertrophied			
				Some generalized dilatation		
				Local "dilatation lesions"		
					PH *	
						NA †

* Pulmonary hemosiderosis associated with distended, thin-walled, arterial vessels throughout the lung.
† Necrotizing arteritis.

of vessel in series of controls.[8] As in the case of arteries and veins, acellular intimal fibrosis is found as a normal age change beyond adolescence. The adventitia is thin. These vessels are associated with the bronchioles, the respiratory bronchioles, and the alveolar ducts.

The elastic pulmonary arteries, defined as vessels greater than 1,000 μ in diameter,[9] differ from muscular pulmonary arteries in that the elastic arteries show a specific pattern of elastic fibrils that predominate in the media.[4] The media of elastic pulmonary arteries is relatively thicker than that of the muscular pulmonary arteries, so that in normal persons it may account for 10 per cent of the external diameter of the vessel. The thickness of the media of the pulmonary trunk and the configuration of its elastic fibrils in control patients of various ages, in patients with pulmonary hypertension present at birth, and in patients with pulmonary hypertension acquired in adult life are considered in detail elsewhere.[4] Intimal age changes occur less frequently in the pulmonary trunk than in the small pulmonary blood vessels.

The media of the normal venule and small vein up to about 200 μ in diameter consists of a single elastic lamina, and that of the vein, greater than 200 or 300 μ, consists of collagen and smooth muscle fibers with admixed elastic laminae that tend to lie concentrically around the walls of the vein. The clear differentiation of media and inner and outer elastic laminae, so characteristic of arteries, is lacking. Venules move away from the air spaces of their respective units to the interlobular septum to form venous trunks. This location is of great importance in distinguishing them from distended thin-walled veinlike arterial vessels found near small bronchi and bronchioles in the severer forms of hypertensive pulmonary vascular disease. Brenner[9] demonstrated that intimal fibrosis occurs universally in adults in all classes of pulmonary blood vessels, especially veins, as a normal age change.

HISTOLOGIC FEATURES OF GRADES OF HYPERTENSIVE PULMONARY VASCULAR DISEASE (TABLE 1)

Grade 1. The Stage of Retention of Fetal-Type Pulmonary Vessels. The definitive histologic features lie in the pulmonary arterioles and the muscular pulmonary arteries. This grade is the earliest ever found in large ventricular septal defect, wide patent ductus arteriosus, or any other congenital cardiac anomaly that allows the pulmonary vascular bed to be subjected to systemic systolic blood pressures from birth.

In the arterioles that normally have a distinct muscular media with internal and external elastic laminae only in the immediate

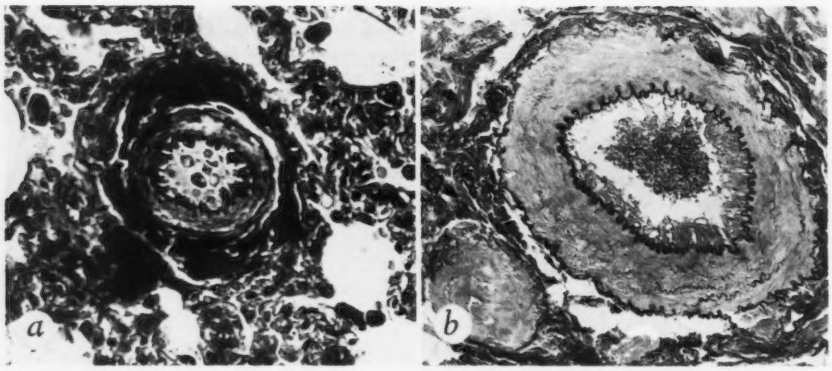

FIG. 1. *a.* Grade 1. Ventricular septal defect type. Transverse section of a pulmonary arteriole with muscular media and internal and external elastic lamina. There is no intimal proliferation. From a boy, aged 1½ years, with ventricular septal defect, corrected transposition, and atrial septal defect. This and all other sections illustrated were stained by Verhoeff's method to demonstrate elastic tissue and counterstained with van Gieson's stain to show muscle and collagen. × 375. *b.* Grade 1. Ventricular septal defect type. Transverse section of a muscular pulmonary artery showing hypertrophy of the media with no intimal reaction. This appearance is characteristic of grade 1, but the dilated, thin-walled branch of the artery containing proliferated endothelium indicates that grade-5 changes were present in this case. This illustrates that the progression of structural changes in pulmonary hypertension is not uniform in individual arteries throughout the lung. From a 34 year old woman having patent ductus arteriosus. × 125.

vicinity of their origins, there is distal extension of muscle. In this way, even arterioles as small as 30 μ look like small muscular pulmonary arteries instead of like veins as they do in the normal lung (fig. 1*a*). The media is relatively thicker than that found in muscular arteries and may be as thick as 25 per cent of the external diameter of the vessel. There is no intimal fibrosis. The adventitia is thick and fibrous. The thickened arterioles also bear a striking resemblance to the intralobular pulmonary arteries of the fetus. It is worthy of comment at this point that comparable classes of vessels differ greatly in size in the fetus and in the adult.

The media of the muscular pulmonary arteries is thickened and may be as thick as 25 per cent of the external diameter (fig. 1*b*). Intimal fibrosis is not present, but the adventitia is thick and fibrous. The medial thickness gradually increases from grade 1 to grade 3, generally speaking, with great variation in the thickness of the individual muscular pulmonary arteries in any one case. As has been suggested previously in a study of the small vessels of the lung in mitral stenosis, this study confirms that there is no clear-cut relation between medial thickness of any one vessel and pulmonary artery blood pressure.[6] The pulmonary veins are normal in ventricular septal defect associated with pulmonary hypertension.

Grade 2. Stage of Medial Hypertrophy with Cellular Intimal Reaction. There is cellular intimal proliferation in the smaller muscular pulmonary arteries, less than about 300 μ in diameter, and the pulmonary arterioles and the lesion may be so marked as to occlude the vessels. There is no intimal reaction elsewhere in the pulmonary arterial tree. Plump endothelial cells that stain brown with van Gieson's stain form only an unduly prominent vascular lining in some arterioles (fig. 2*a*). In other vessels they have proliferated to the extent of forming characteristic eccentric masses with underlying material staining brown with van Gieson's stain (fig. 2*b*). This proliferated intimal material may coalesce

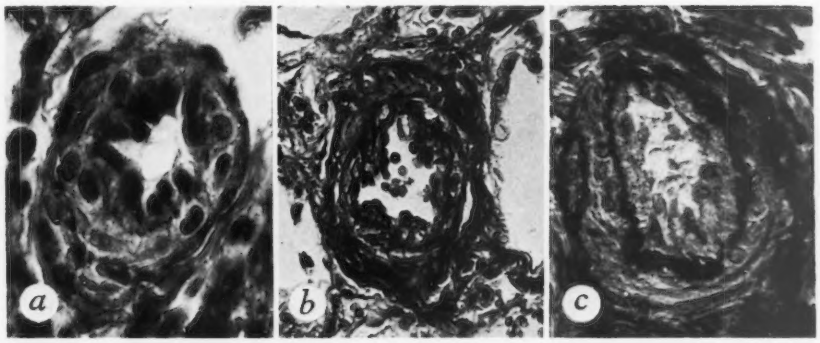

FIG. 2. *a*. Early grade 2. Transverse section of a pulmonary arteriole with plump, endothelial cells that form only an unduly prominent vascular lining. From a 4 year old boy with patent ductus arteriosus. × 700. *b*. Grade 2. Transverse section of a pulmonary arteriole with a muscular media and eccentric endothelial masses with underlying material staining brown with van Gieson's stain. From a 37 year old woman with atrial septal defect. × 375. *c*. Grade 2. Transverse section of a pulmonary arteriole with proliferated endothelium and material staining brown with van Gieson's stain forming a concentric rim around the circumference. From a 4 year old boy with patent ductus arteriosus. × 435.

and lead to vascular occlusion. In some cases the proliferated endothelium and material staining brown with van Gieson's stain may form a concentric rim around the circumference (fig. 2*c*). In time, fibrous tissue, recognizable by its property of staining red with van Gieson's stain, forms beneath the endothelium and this constitutes the earliest stage of grade 3.

Grade 3. Stage of Progressive Fibrous Vascular Occlusion. In this grade there is progressive intimal fibrosis in the smaller (300 μ) muscular pulmonary arteries and pulmonary arterioles with a change in the nature of the intimal proliferation and an extension of it into medium-sized (300 to 500 μ) arteries. The intimal proliferation seen in early lesions of grade 3 represents a change from the predominantly cellular endothelial reaction seen in grade 2 to one that consists of cellular fibrous tissue as judged by its tinctorial properties (fig. 3*a*). Later lesions are characterized by concentric or eccentric masses of less cellular fibrous tissue that stains bright red with van Gieson's stain. Old intimal fibrotic lesions show an admixture of fine or even coarse elastic fibrils and some splitting or elastosis of the internal elastic lamina, while the fibrous tissue may be relatively acellular. Running parallel with these characteristic changes in the histologic structure of the intimal fibrous tissue is its equally characteristic extension.

Most of the intimal lesions are first found in the arterioles and smaller muscular pulmonary arteries and extend back around the mouths of origin of the vessels and involve the parent muscular arteries (fig. 3*b*). In many instances, however, heaped up intimal fibrotic lesions are found early in a muscular pulmonary artery in proximity to the origin of an arteriole. It has already been pointed out that arterioles may rise at a proximal point in the pulmonary vascular tree as right-angled branches of fairly large muscular arteries. They also may arise distally as terminations of the arteries. Intimal fibrosis is found first in both sites. Only in severer cases of pulmonary hypertensive change is widespread intimal fibrosis found in the medium-sized muscular pulmonary arteries.

Serial sections demonstrate the plaques of intimal fibrous tissue in muscular arteries are focal (fig. 3*a*). In some instances these foci of intimal fibrous tissue are continuous with the fibrous tissue in the smallest muscular

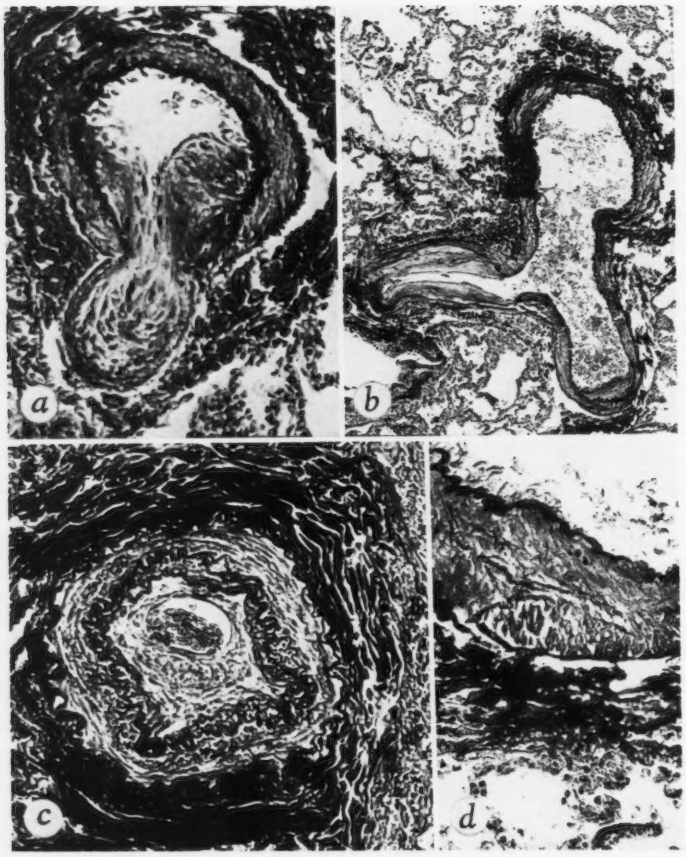

FIG. 3. *a*. Grade 3. Transverse section of a small muscular pulmonary artery with an oblique section of an arteriolar branch. There is medial hypertrophy in the artery. Cellular fibrous tissue forms eccentric masses in the artery and occludes the arteriole. From a 9 year old boy having cor triloculare biatriatum without pulmonary stenosis. × 160. *b*. Grade 3. Transverse section of a medium-sized muscular pulmonary artery and oblique sections of 2 of its branches. The parent artery shows hypertrophy of the media but no intimal reaction. The smaller branch shows some dilatation with thinning of the media and acellular intimal fibrosis. From a 6 year old girl with ventricular septal defect. × 30. *c*. Grade 3. Transverse section of a medium-sized muscular pulmonary artery. There are medial hypertrophy and severe intimal fibrosis so that only a small eccentric endothelium-lined channel remains patent. There is elastosis of the internal elastic lamina. From a girl, aged 6½ years, with ventricular septal defect and patent ductus arteriosus. × 175. *d*. Portion of wall of large muscular pulmonary artery showing fasciculi of longitudinal muscle in close apposition to the external elastic lamina. This case had grade-5 structural changes in the small pulmonary vessels, but the appearances are equally characteristic of any of the grades from 3 to 6. From a 27 year old woman with atrial septal defect. × 200.

arteries and the arterioles but in others there is no connection. Finally, the concentric or eccentric masses of avascular fibrous tissue in the muscular arteries and pulmonary arterioles may completely occlude the vessel, but a small endothelium-lined channel with an irregular course frequently remains patent (fig. 3*c*). Thus the characteristic feature of

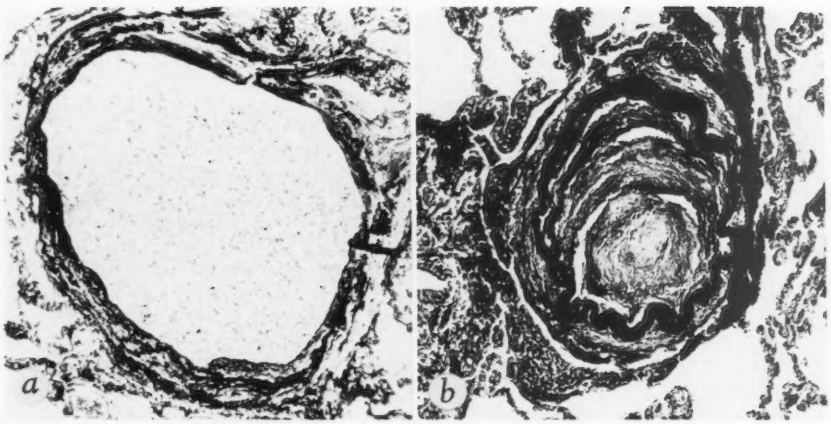

FIG. 4. Generalized dilatation may develop in any of the lesions from severe grade 3 to grade 6. *a*. Grade 3. Transverse section of a dilated muscular pulmonary artery. There is no intimal fibrosis. × 60. *b*. Grade 5. Transverse section of a dilated, muscular pulmonary artery. There is severe intimal fibroelastosis and the internal elastic lamina is grossly thickened. The media is thin and is encroached upon by the intimal fibrosis. From a 24 year old woman with patent ductus arteriosus. × 100.

severe hypertensive pulmonary vascular disease, grade 3, is the widespread occlusion of muscular pulmonary arteries less than about 500 μ in diameter and of arterioles by acellular fibrous tissue admixed with fine elastic fibrils. The large muscular arteries more than about 600 μ in external diameter rarely show intimal fibrosis even when the smallest and medium-sized arteries and arterioles show foci of complete occlusion. Atheroma rather than intimal fibrosis is found in the large muscular and elastic pulmonary arteries in the presence of severe pulmonary hypertension.[3]

In grade 3 the media reaches the limit of its capacity for hypertrophy, so that its thickness may be up to 30 per cent of the external diameter of the vessel. The media of the arteriole is similarly much thickened. In the medium-sized and large muscular arteries the increase in medial thickness is brought about partly by the development of fasciculi of longitudinal muscle which usually lie in close apposition to the internal or external elastic lamina and which are bounded by elastic laminae as shown in figure 3*d*. Occasionally increased numbers of longitudinal muscle fibers, not in distinct fasciculi delineated by elastic fibrils, may be seen in the media itself.

Although the characteristic feature of grade 3 is medial hypertrophy, some thinning of the media is seen also in the severer, late stages of this grade. This dilatation occurs in patent vessels (fig. 4*a*) and those showing focal areas of occlusion (fig. 4*b*). In the latter case, the dilatation of vessels with thinning of the media is found in smaller muscular arteries and arterioles either at or distal to a focus of fibrotic occlusion of a parent muscular artery, and in medium-sized arteries, proximal to the foci of occlusion. In the former site the thinning is probably a type of disuse atrophy subsequent to the lowering of blood pressure distal to the fibrotic occlusion and is analogous to the thinning of pulmonary arteries in pulmonary stenosis. In the latter site the dilatation is an expression of decompensation to the severely elevated pulmonary resistance.

Dilatation Lesions. In addition to the generalized dilatation that occurs in severe examples of grade 3 and in grades 4, 5, and 6, excessive dilatation occurs in some of the smallest muscular pulmonary arteries and the arterioles to form distended sacs. In many of these microaneurysms there is endothelial proliferation and at times superadded throm-

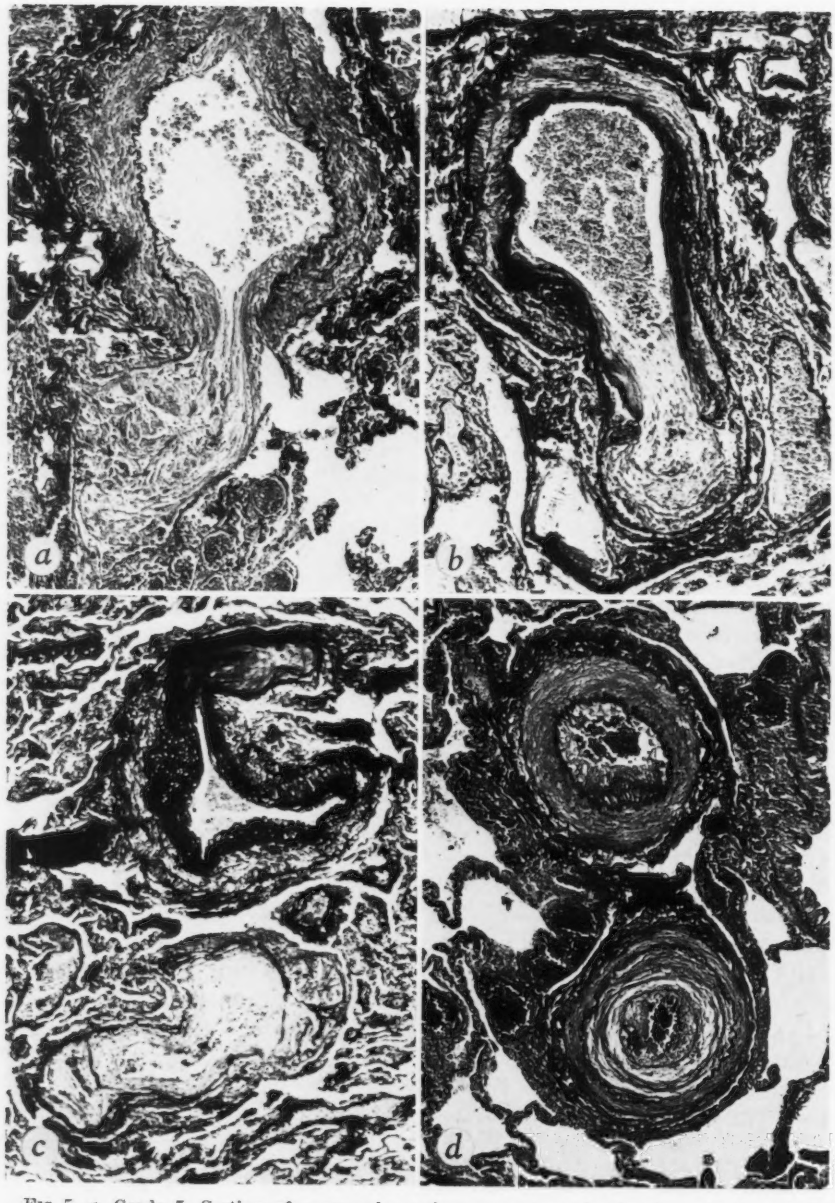

FIG 5. *a.* Grade 5. Section of a muscular pulmonary artery showing hypertrophy of the media and excessive dilatation of an arteriolar branch to form a plexiform lesion. The intimal proliferation in the distended sac is cellular indicating the dilatation lesion to be of recent formation. From a 27 year old woman with atrial septal defect. × 150. *b.* Grade 5. Section of a muscular pulmonary artery showing hypertrophy of the media, with the development of longitudinal muscle, and a plexiform lesion. The cellular proliferation in the dilatation lesion is partially replaced by fibrous tissue indicating that it is older

(Continued on opposite page)

bosses. These complex vascular formations consisting of severely dilated vessels with internal cellular proliferations we term "dilatation lesions," and they are to be distinguished from the generalized dilatation that occurs throughout the pulmonary vasculature in some stages of pulmonary hypertension. These dilatation lesions are seen in 4 main forms: (1) plexiform lesions, (2) veinlike branches of hypertrophied, usually occluded, muscular pulmonary arteries, (3) angiomatoid lesions, and (4) cavernous lesions.

1. The Plexiform Lesion. The pulmonary arterioles and smallest muscular pulmonary arteries are greatly distended to form sacs whose walls are fragile, consisting of a single elastic lamina or an exceedingly thin layer of muscle between 2 ill-defined elastic laminae (fig. 5*a*). Large similarly thin-walled channels leave these dilated sacs and terminate as capillaries that pass to the alveolar walls. In some instances vessels of capillary size leave the sacs and pass directly to the alveolar capillaries. As a result of endothelial proliferation and thrombosis in these dilated vessels, 3 zones, frequently well defined, may be seen in them. Proximally there is fibrous tissue continuous with that in the intima of the patent muscular pulmonary artery. In early lesions this fibrous tissue is cellular; in late lesions it is acellular. There is a central zone of proliferative cellular endothelial tissue which often assumes a characteristic plexiform pattern in the sac so that this lesion might conveniently be termed the "plexiform lesion." It is the hallmark of grade 4. Distally, in the distended sac, there is frequently a thrombus, stimulated probably by the papilliferous endothelial proliferation. As the lesion ages, the fibrosis spreads through it and finally replaces it (fig. 5*b* and *c*).

2. Veinlike Branches of Hypertrophied Muscular Pulmonary Arteries (fig. 6*a* and *b*). Muscular pulmonary arteries, which show medial hypertrophy and gross intimal fibroelastosis, give rise to thin-walled branches resembling veins, and these end as capillaries in the alveolar walls. Such veinlike structures usually emerge from the parent muscular pulmonary artery proximal to the point of obstruction and have been considered to represent a collateral pulmonary blood flow to the alveolar walls.[10] In the present cases, however, some of these dilated branches were found to arise from vessels with patent lumens.

3. The Angiomatoid Lesion (fig. 6*c*). In this instance muscular pulmonary arteries showing intimal fibrosis give rise to thin-walled vessels. The latter show peculiar vascular formations within their lumens. Cross sections of these formations show them to be composed of a series of thin blood vascular structures having walls of simple elastic tissue. These intraluminal vessels leave the arteries containing them to form a surrounding angiomatoid mass. Since the angiomatoid structure surrounds the dilated vessel it lies somewhat removed from the muscular artery that gave rise to the dilated branch. The angiomatoid lesion itself gives rise to many thin-walled vessels which ramify in all directions in the pulmonary substance to supply capillaries to the air spaces. If the intimate connection between parent muscular pulmonary artery, thin-walled branch, and angiomatoid lesion is not established by examination of serial sections, one may mistakenly consider the angiomatoid mass to be an independ-

than the corresponding lesion shown in figure 4*c*. From a 24 year old woman with patent ductus arteriosus. × 75. *c*. Grade 5. Section of a muscular pulmonary artery showing an old plexiform lesion. Gross elastosis of the internal elastic membrane of the artery has developed and the proliferated tissue in the dilated sac has been totally replaced by fibroelastic tissue. From a 20 year old woman with patent ductus arteriosus. × 75. *d*. Transverse section of a parent muscular pulmonary artery that shows hypertrophy of the media and intimal fibrosis, and one of its branches which is dilated and almost totally occluded by fibrous tissue showing a so-called onion-layering configuration. From a 27 year old woman with a common atrioventricular canal with no subvalvular communication. × 75.

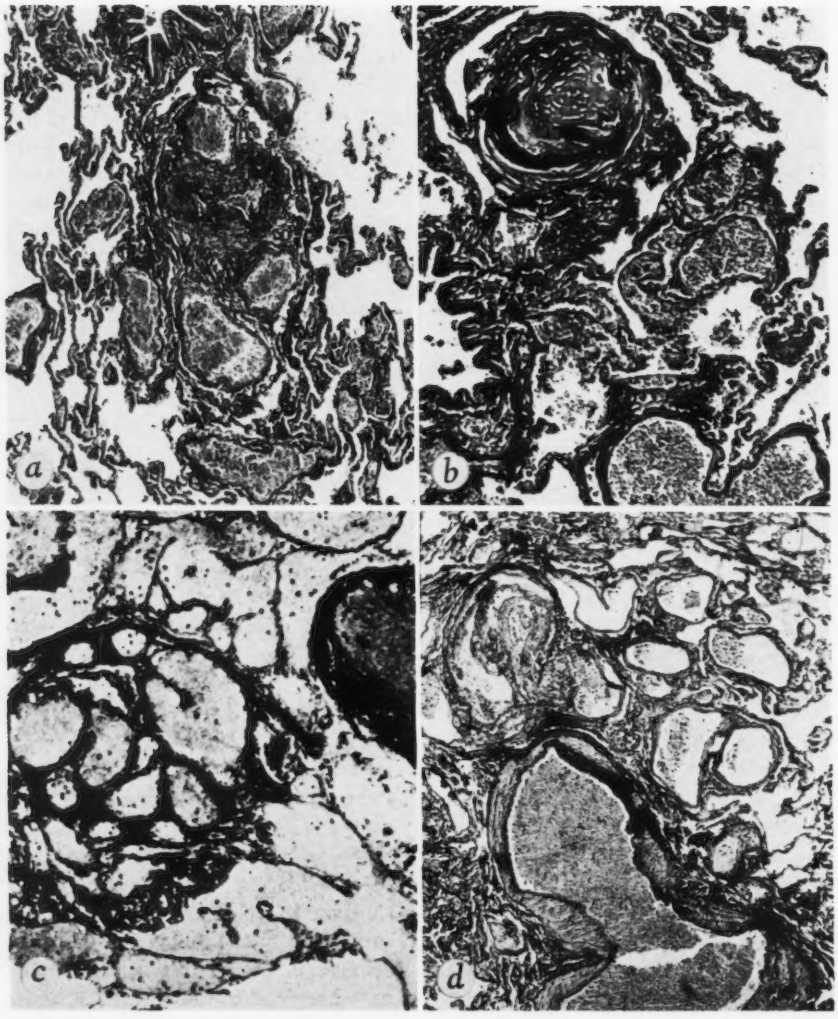

FIG. 6. *a*. Grade 5. Transverse section of a muscular pulmonary artery, showing hypertrophy of the media and obliteration of its lumen by fibrous tissue, and its veinlike, thin-walled branches which cluster characteristically around the parent vessel. From a 24 year old woman with patent ductus arteriosus. × 75. *b*. Grade 5. Transverse section of a muscular pulmonary artery, showing obliteration of its lumen by dense acellular fibrous tissue. There are gross thickening and elastosis of the internal elastic lamina. The media is largely replaced by fibrous tissue. Clustering near the artery are its thin-walled, veinlike branches. From a 24 year old woman with patent ductus arteriosus. × 75. *c*. Grade 5. Transverse section of the angiomatoid form of dilatation lesion. The thin-walled, veinlike branches of a hypertrophied muscular pulmonary artery form an angiomatoid mass in the lungs. From a 32 year old woman with ventricular septal defect. × 100. *d*. Grade 5. Section of lung showing a cavernous dilatation lesion. Cavernous thin-walled branches, one showing endothelial proliferation, are seen clustered around the hypertrophied parent muscular pulmonary artery. From a 24 year old woman with patent ductus arteriosus. × 75.

ent separate entity in the pulmonary substance. The diameter of this structure approaches 1 mm.

4 The Cavernous Lesion (fig. 6*d*). Intermediate between the 2 forms previously described, this form of lesion is composed of cavernous vessels that arise from a thin-walled branch of a muscular pulmonary artery.

All 4 types of dilatation lesions are simply severer and more complex expressions, in the pulmonary arterioles and the smallest pulmonary arteries, of the generalized dilatation that occurs throughout the pulmonary vasculature as a result of the chronically high vascular resistance. Early generalized dilatation is seen in association with the predominantly hypertrophied vessels in a late stage of grade 3, but the appearance of the plexiform lesion is the hallmark of grade 4. In severer examples of grade 4 and in grade 5, the generalized dilatation of pulmonary arteries also proceeds. Grade 5 is characterized by the appearance of many veinlike branches of hypertrophied arteries and the angiomatoid and cavernous lesions, all of which give rise to sinusoid-like vessels throughout the pulmonary substance. The angiomatoid lesion is rare and was not seen in the Mayo Clinic series reported herein. The case included for the sake of completion was one of ventricular septal defect with pulmonary hypertension studied by one of us (D.H.) in association with Dr. D. B. Brewer at the University of Birmingham, England.

Grade 4. Stage of Progressive Generalized Arterial Dilatation with the Formation of Complex Dilatation Lesions (Plexiform Lesions). In grade 4 the emphasis in the histologic picture shifts from predominant signs of hypertrophy to those of dilatation. Both the muscular pulmonary arteries and the arterioles show progression in the dilatation that was seen to originate in the late stages of grade 3. The hallmark of grade 4 is the appearance of the plexiform type of dilatation lesions described in the previous section (fig. 5*a*, *b*, and *c*). In addition, segments of branches of hypertrophied arteries dilate (fig. 5*d*).

A distended sac is formed but the wall consists of a thin but still recognizable arterial structure with a distinct media and internal and external elastic laminae. In such dilated arteries intimal thickening may occur. The intimal tissue is fibrous and the fibers and nuclei tend to be arranged concentrically to give a so-called onion-layering appearance (fig. 5*d*). Beyond the distended segment of the artery, the normal arterial structure is resumed with superadded intimal fibrosis. Many muscular arteries and arterioles in grades 4 to 6 still show marked increase in medial thickness with gross intimal fibroelastosis.

Grade 5. Stage of Chronic Dilatation with Formation of Numerous Dilatation Lesions and Pulmonary Hemosiderosis. This is the stage of dilatation in which the vessels show medial as well as intimal fibrosis and look rigidly dilated. The media of the muscular pulmonary arteries and the arterioles is thinned and fibrosed and in many cases, the intimal fibrous tissue is acellular or even hyaline. In grades 3 and 4, as previously mentioned, arteries with intimal fibrosis show small endothelium-lined channels as the remainder of a lumen all but obliterated by fibrous tissue. In grade 5, however, some of such central channels are widely dilated and surrounded by what appears to be a rigid tube consisting largely of acellular fibrous tissue and a thin, fibrosed media. The arterioles show similar dilatation with fibrosis.

All 4 types of dilatation lesions, that is, the simple veinlike branch of the hypertensive muscular pulmonary artery, the plexiform lesion, the angiomatoid lesion, and the cavernous lesion, are commonly found and give rise to thin-walled, dilated vessels which ramify throughout the lung rendering it highly vascular and filled with sinusoid-like vessels (fig. 7*a*). It would seem that these are fragile and either burst or allow diapedesis of blood, for foci of hemosiderosin-containing macrophages are scattered throughout the lung in grade 5 (fig. 7*b*).

Grade 6. Stage of Necrotizing Arteritis. Few patients with hypertensive pulmonary vascular disease ever show the vascular

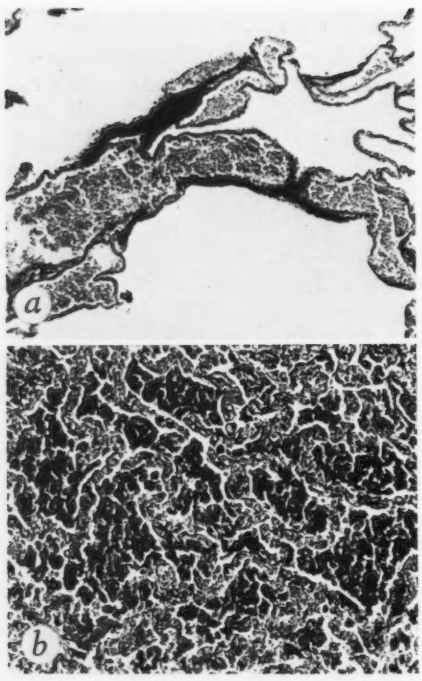

FIG. 7. *a*. Transverse section of a lung showing one of the numerous thin-walled, sinusoid-like vessels which are branches of hypertrophied muscular arteries and which characterize grade 5. From a 21 year old man with ventricular septal defect. ×100. *b*. Grade 5. Transverse section of lung showing the pulmonary hemosiderosis which results from bleeding from thin-walled vessels as shown in figure 7*a*. From a 23 year old man with idiopathic pulmonary hypertension. ×100.

changes in the lung that we include in grade 6. In fact, the only patient of the present series who had this group of histologic features characterized by necrotizing arteritis in its acute and subacute forms was suffering from an unusual form of atrial septal defect associated with pulmonary hypertension from birth. There is justification for including this case at this point to illustrate this grade of hypertensive pulmonary vascular disease, for necrotizing arteritis has been observed in ventricular septal defect with pulmonary hypertension.[11] It is at the same time necessary to point out that necrotizing arteritis is uncommonly reported with any type of cardiac disease; a few cases have been reported in mitral stenosis associated with pulmonary hypertension and in idiopathic pulmonary hypertension.

In necrotizing arteritis some of the muscular pulmonary arteries show acute fibrinoid necrosis. In sections stained with hematoxylin and eosin the muscle has a glassy appearance with loss of nuclei or has smudgy staining. The typical staining reactions for fibrinoid are given. Vessels show complete necrosis of muscle with a surrounding inflammatory reaction consisting predominantly of polymorphonuclear leukocytes with a few eosinophils.

Many arteries exhibit the subacute or healing phase of arteritis with masses of young basophilic cellular fibrous tissue replacing the dead muscle and forming masses in proximity to it in the intima and adventitia. The masses of fibrous tissue in the intima appear to be reactive to the underlying medial necrosis and, being basophilic and cellular, form a striking contrast to the pre-existing intimal fibrous tissue, which is eosinophilic and relatively acellular. Thrombosis is found in some arteries, many of which show gross hypertrophy. The granulation tissue may replace as much as a third of the media (fig. 8*a*) and in exceptional circumstances, the entire vessel may be replaced by granulation tissue, only the elastic laminae retaining partial integrity (fig. 8*b*). In other cases, only a small arc of the media is replaced by fibrous tissue so that, lying between the bulbous expansions in the intima and adventitia, this gives the lesion a dumbbell shape. In the connecting bar of fibrous tissue in the media, the long axes of the fibroblast nuclei are radial.

The adventitial masses of granulation tissue lie around branches of arteriolar size, and endothelium-lined channels of this magnitude enter the fibrotic region but become lost therein. Many small capillaries, lined by plump endothelium and containing erythrocytes, ramify throughout the basophilic fibrous tissue and a few thin-walled vessels leave this tissue to lie between the old acellular collagen fibers of the adventitia (fig. 8*a* to *d*).

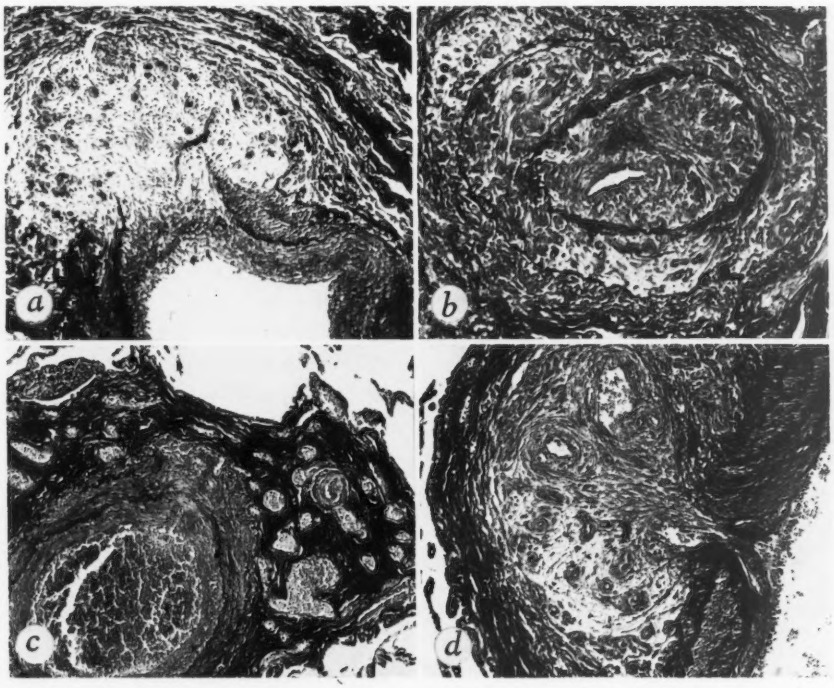

FIG. 8. All photomicrographs are transverse sections of muscular pulmonary arteries from a 27 year old man who had an unusual form of atrial septal defect considered to have been associated with pulmonary hypertension from birth. All show subacute necrotizing arteritis, a change pathognomonic of grade 6. *a*. Section showing medial hypertrophy, acellular intimal fibrosis, and replacement of an arc of the media by granulation tissue with prominent blood capillaries. × 75. *b*. Granulation tissue replaces the media, forms masses in the adventitia, and almost totally occludes the lumen. In this instance the entire media had undergone necrosis × 175. *c*. Prominent, dilated vessels in the adventitia that are derived from granulation tissue. × 125. *d*. The mass of granulation tissue in the adventitia is around the origin of an arteriole, indicating this to be a site of predilection for necrotizing arteritis. The granulation tissue contains large capillary vessels. × 100.

This imparts a characteristic picture of many dilated veinlike structures lying scattered throughout the adventitia of the larger muscular pulmonary arteries (fig. 8*c*).

The site of masses of adventitial fibrous tissue lying around branches of the muscular pulmonary arteries again suggests that the junction of artery and arteriole is a site of predilection for arteritis just as has been found for intimal fibrosis and the so-called dilatation lesions (fig. 8*d*).

Grade 1 in Atrial Septal Defect. In atrial septal defect, and those other forms of congenital heart disease characterized by the presence of high pulmonary blood flow over a prolonged period prior to the onset of pulmonary hypertension, the structural changes in grade 1 differ from those seen in ventricular septal defect. Initially, before the onset of pulmonary hypertension, the pulmonary arterioles are lined by a single elastic lamina as in the normal person.

Both they and the small muscular pulmonary arteries are widely dilated. Even at this stage where the pulmonary arterial blood pressure is normal or only slightly elevated, the pulmonary veins are the site of pronounced, intimal acellular fibrosis. This

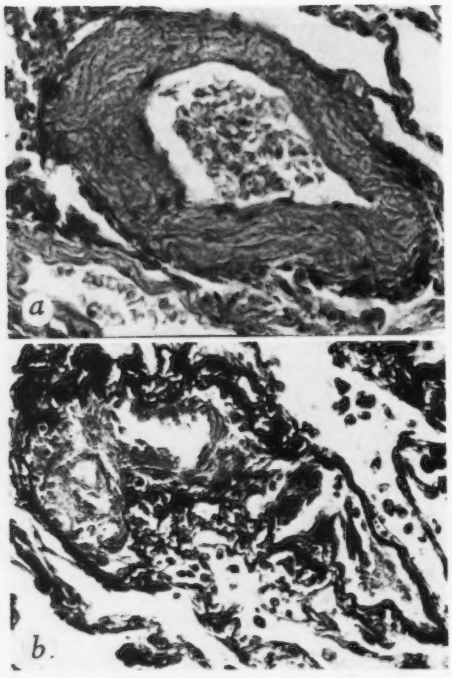

FIG. 9. *a*. Transverse section of a pulmonary vein showing severe acellular intimal fibrosis. From a 50 year old man with atrial septal defect and mitral stenosis. The lesion is characteristic for cases of atrial septal defect. The existing mitral stenosis is considered of incidental significance as regards this lesion. × 365. *b*. Grade 1. Atrial septal defect type. Oblique section of a dilated arteriole showing endothelial proliferation. The arteriole has no muscular media. From a 34 year old man with atrial septal defect and moderate pulmonary hypertension. × 250.

venous intimal change remains characteristic of atrial septal defect with all grades of changes in the pulmonary arteries (fig. 9*a*).

Associated with the onset of pulmonary hypertension is a pronounced cellular endothelial reaction in the arterioles and the smallest muscular pulmonary arteries, so that vascular occlusion by intimal proliferation appears to be the origin of the increased pulmonary vascular resistance (fig. 9*b*). Once pulmonary hypertension is established, a distinct muscular media forms in the arterioles and there is hypertrophy of the media of the muscular pulmonary arteries. These histologic features are the same as those seen in hypertensive pulmonary vascular disease, grade 2, associated with ventricular septal defect, and from this point the progression of structural changes is identical with that already described.

SUMMARY

Progressive histologic changes occur in the media and intima of pulmonary arteries and arterioles in the presence of chronic elevation of pulmonary artery blood pressure complicating congenital septal defects. This progression is so stereotyped as to allow a division of the structural effects of the hypertension into 6 grades. The classification is based on the study of lungs from 67 patients having congenital heart disease, and 2 having idiopathic pulmonary hypertension. Pulmonary arterial hypertension was demonstrated at cardiac catheterization in 55 instances and was inferred from the clinical and pathologic features in 9 others. The classification is as follows:

Grade 1. In large ventricular septal defect and wide patent ductus arteriosus: medial hypertrophy in arteries and arterioles; no intimal changes. In atrial septal defect: cellular, intimal proliferation in the smallest muscular arteries and the arterioles; intimal fibrosis in pulmonary veins.

Grade 2. Medial hypertrophy; cellular intimal proliferation.

Grade 3. Medial hypertrophy; intimal fibrosis; early generalized vascular dilatation in severe instances.

Grade 4. Progressive generalized vascular dilatation and occlusion by intimal fibrosis and fibroelastosis. Appearance of the plexiform lesions, which are one form of the complex dilatation lesions that occur in the pulmonary arterioles and the smaller muscular pulmonary arteries.

Grade 5. Appearance of the other "dilatation lesions," including veinlike branches of hypertrophied muscular arteries, cavernous lesions, and angiomatoid lesions; highly vascular lung due to veinlike arterial branches; pulmonary hemosiderosis.

Grade 6. Necrotizing arteritis.

Summario in Interlingua

Progressive alterationes histologic occurre in le tunicas medie e intime del arterias e arteriolas pulmonar in le presentia de elevation chronic del pression de sanguine pulmono-arterial que complica congenite defectos septal. Iste phenomeno es si stereotype que nos pote divider le effectos structural del hypertension in 6 grados successive. Lor definition es basate super le studio del pulmones de 67 patientes con congenite morbo cardiac e de 2 con idiopathic hypertension pulmonar. Hypertension pulmono-arterial esseva demonstrate per catheterisation cardiac in 55 casos e esseva presumite super le base de observationes clinic e pathologic in 9 alteres. Le classification es le sequente:

Grado 1. In casos de grande defectos ventriculo-septal e de marcate patente ducto arteriose: Hypertrophia medial in le arterias e arteriolas; nulle alterationes del intima.– In casos de defecto atrio-septal: Proliferation cellular del intima in le plus miere arterias muscular e in le arteriolas; fibrose intimal in le venas pulmonar.

Grado 2. Hypertrophia medial; proliferation cellular del intima.

Grado 3. Hypertrophia medial; fibrose intimal; precoce generalisate dilatation vascular in casos grave.

Grado 4. Progressive dilatation vascular generalisate e occlusion per fibrose e fibroelastose intimal. Apparition del lesiones plexiforme, le quales representa un del formas del complexe lesiones de dilatation occurrente in le arteriolas pulmonar e in le minor arterias pulmonar muscular.

Grado 5. Apparition del altere "lesiones de dilatation," incluse brancas venoide de hypertrophiate arterias muscular, lesiones cavernose, e lesiones angiomatoide; pulmon altemente vascularisate in consequentia del venoide brancas arterial; hemosiderosis pulmonar.

Grado 6. Arteritis necrotisante.

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The Electrocardiographic Findings in Small, Atypical Myocardial Infarcts

By A. Henry Clagett, Jr., M.D.

Others have described mild or atypical myocardial infarction as a clinical condition in which the pain is of short duration and the evidence of tissue damage is slight. It occurs in otherwise healthy individuals and is characterized by complete recovery and the absence of complications. In this study the electrocardiograms of 359 patients with myocardial infarction were divided according to the QRS complexes; one group showing normal QRS complexes and the other showing typical Q waves. The clinical features of the patients in these two groups were compared.

IN a recent article on "mild" myocardial infarction, Prinzmetal, Weiner, and Bhuyan[1] describe the clinical features of this condition as follows: pain of short duration occurring in a young or middle-aged healthy man with no evidence of previous heart disease, hypertension, diabetes, or other chronic illness. Shock never occurs and evidence of tissue damage (fever, leucocytosis, sedimentation rate, serum transaminase level) is either absent or slight. There is no cardiac enlargement, no congestive failure and no arrhythmias. In several days the patient looks and feels well. They say that normal or abnormal, the electrocardiogram rarely provides evidence concerning the severity of an infarction.

This subject was introduced by Papp and Smith in 1951,[2] when, in a series of 109 patients with myocardial infarction, they found 33 who could be classified as "slight" on clinical grounds. These consisted of absence of shock or failure, evidence of necrosis slight or absent, and an uncomplicated recovery in each instance. In 35 attacks the electrocardiogram was mentioned as showing a small or absent R wave in 3 and significant Q waves in 7. The electrocardiogram returned to normal in 14, showed improvement in 14, was unchanged in 6, and became worse in 1.

Littmann and Barr[3] reported a total of 209 cases of coronary disease, 11 of which were classified as atypical (small, obscure) infarcts. These patients gave no history of previous infarction although 4 had a history of angina. None had shock, myocardial failure, or thromboembolism. There were no deaths. Ten had fever exceeding 99.6 F. The white blood count varied from 7,700 to 19,200, averaging 12,200. The sedimentation rate was increased in all cases. Two patients had recurrences and progressed to typical infarction.

Cutts, Merlino, and Easton[4] recently reported 79 patients with coronary type chest pain whose electrocardiogram showed inverted T waves in the chest leads without QRS abnormalities. In one third of these patients the electrocardiogram returned to normal. After an average follow-up of 4 years, 24 patients had died. Eleven patients were examined post mortem and all showed marked narrowing of the coronary arteries. Several cases showed small healed infarcts while others showed focal necrosis surrounded by normal myocardium.

The paper of Papp and Smith[2] was the stimulus in 1953 for a review of 359 patients with myocardial infarction at the Memorial Hospital. These were consecutive cases, unselected except for the following criteria: a typical history of persistent retrosternal pain lasting at least an hour, usually lasting until relieved by hypodermic injection; occurrence of this episode within 2 weeks of hospital admission* (usually admitted the same day);

From the Cardiovascular Section, Memorial Hospital, Wilmington, Del.

*The time was extended to 2 weeks to include some patients with late development of electrocardiographic changes who were treated at home while the electrocardiogram was normal.

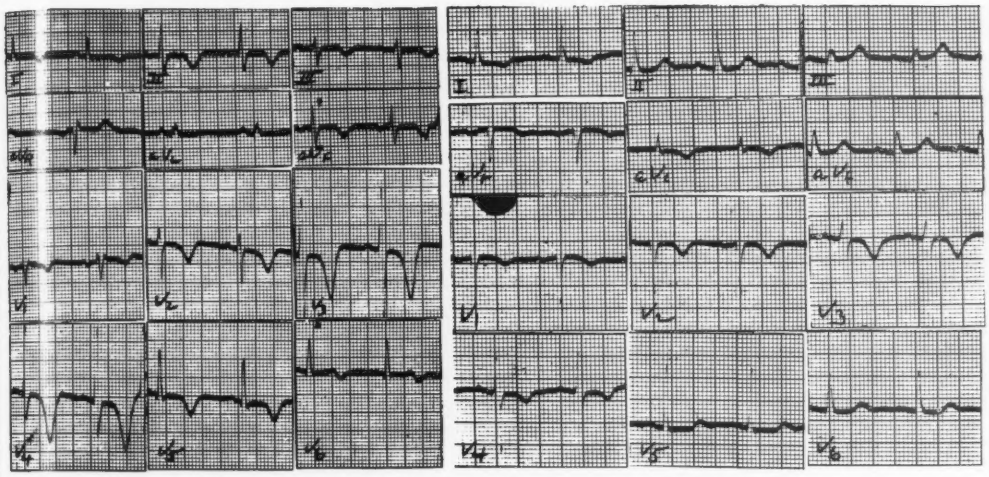

FIG. 1 *Left.* Case 14. Electrocardiogram taken February 23, 1953.
FIG. 2 *Right.* Case 17. Electrocardiogram taken February 25, 1952. A tracing taken March 4, 1952 showed much less T-wave inversion.

evidence of tissue damage (fever, leukocytosis, increased sedimentation rate); abnormal electrocardiogram.

In previous studies[2, 3] the diagnosis of small or atypical myocardial infarction was made on clinical grounds and the electrocardiographic findings were then described.*

In this study the electrocardiograms were divided into those with significant Q waves (typical) and those with normal QRS complexes (atypical). The clinical data were then correlated with these findings.

ILLUSTRATIVE CASES

Case 14. An 84-year-old white man was in excellent health until February 8, 1953, when he was seized with a severe squeezing retrosternal pain while taking a walk after breakfast. He vomited 3 times but the pain persisted until he received an injection about 1 hour later. His electrocardiogram showed normal QRS complexes with inverted T waves in leads aV_L, V_2, and V_3. His temperature was normal except for 99 F. on February 10. On February 11 his sedimentation rate was 23 mm. per hour. On the same day a tracing showed the T waves to be more deeply inverted in leads I, II, aV_F, and V_1 to V_5 inclusive; the QRS complexes remained normal.

On February 13 he had a recurrence of the retrosternal pain, which was relieved only following the administration of meperidine (Demerol).

A tracing taken on February 23 (fig. 1) showed less T-wave inversion in lead I but more in the other leads; the QRS complexes remained normal.

The patient was discharged from the hospital, improved, on February 25. At present, he is living and well at 88 years of age. He has had no recurrence of this condition.

Case 17. A 58-year-old woman was admitted to the hospital on February 23, 1952. She had been healthy except for arterial hypertension for approximately 2 years. Her sister died 3 days before admission; this upset the patient.

At 2 a.m. on the day of admission she was wakened by a severe tightness in the chest. She arose and walked about the room in an attempt to relieve the pain but it persisted until she was given morphine, about 1 hour later. The pain was accompanied by dyspnea. Her electrocardiogram on

*The work of Cutts and his colleagues[4] was somewhat similar to this study inasmuch as the patients were selected by electrocardiographic criteria; a major difference is that the present study excluded those patients who showed no evidence of tissue damage. The work of Prinzmetal et al.[1] also included patients with evidence of no tissue damage.

TABLE 1.—*Data Concerning Patients with Small Atypical Infarcts*

No.	Sex	Age	Date	Location Ant.	Post.	Follow-up
1	M	59	Sept. 1953		x	
2	M	62	Mar. 1949	x		Died June 1949
3	M	54	Sept. 1950	x		Healthy except coronary insufficiency, November 1957
4	M	39	Oct. 1952	x		Living and healthy
5	M	48	Jan. 1949		x	
6	M	39	May 1949	x		Living and well—no recurrence
7	F	71	Nov. 1951	x		Angina and 1 infarct; living
8	M	64	May 1953	x		
9	M	57	July 1951		x	Living
10	M	45	June 1953	x		Living; no recurrence—occasional angina
11	M	48	Feb. 1953	x		Died of acute infaret 1 year later
12	M	59	Dec. 1949		x	Recurrence in 1950
13	M	41	July 1951		x	Healthy; living—no recurrence
14	M	84	Feb. 1953	x		Healthy—no recurrence
15	F	52	April 1952	x		Died of cerebral thrombosis—May 1957
16	F	65	Dec. 1949	x		Died; postoperative—Jan. 1950
17	F	58	Feb. 1952	x		Died in heart failure—second coronary 1952
18	F	75	Mar. 1949	x		Died of malignancy, 1951
19	F	77	Feb. 1951		x	Diabetic—died in attack
20	M	43	Jan. 1949	x		Died prior to 1952
21	M	54	May 1951	x		Living and well; no recurrence—mild angina
22	M	60	Dec. 1949	x		
23	M	58	Oct. 1953		x	
24	F	71	Nov. 1949	x		
25	F	47	April 1953	x		Subsequent episode of coronary insufficiency
26	M	51	Dec. 1953	x		Living and well—no recurrence
27	M	57	Jan. 1953	x		
28	M	57	Mar. 1953	x		
29	M	60	May 1949		x	Subsequent transmural infaret; Jan. 1952—Sept. 1952—May 1956, died
30	M	38	Nov. 1953	x		Two subsequent infarets—living
31	F	65	Dec. 1950	x	x	Small anterior Dec. 1950; large posterior Dec. 1952; living—no recurrence
32	M	59	Jan. 1950	x		
33	M	53	Dec. 1949	x		Living—no recurrence
34	F	66	July 1953		x	Died, July 1957
35	F	55	May 1949	x		Healthy—no recurrence
36	M	57	Dec. 1953		x	Healthy—no recurrence
37	F	66	Mar. 1952	x		Died 1957; second coronary—severe diabetes
38	M	48	Dec. 1953		x	Healthy—no recurrence
39	F	58	Dec. 1949	x		
40	M	64	April 1953	x		Died of staph. infection, Aug. 1957
41	F	63	June 1950	x		Died, 1954
42	F	72	April 1953		x	Healthy—no recurrence
43	M	63	May 1953		x	Died, March 1956
44	M	51	Jan. 1949	x		Died 1952; second infaret

TABLE 1.—(*Continued*)

February 23 showed normal QRS complexes with inverted T waves in leads aV_L and V_1 to V_4 inclusive.

Her sedimentation rate on February 24 was 25 mm. per hour; subsequent readings were 24, 28, and 21 mm. per hour. She was afebrile except for a temperature of 99.2 F. during the first 4 days.

Her tracing on February 25 (fig. 2) showed an increase in the degree of T-wave inversion; the QRS complexes remained normal. The next tracing on March 4, showed less T-wave inversion. She was discharged improved on March 19.

TABLE 2.—*Analysis of Frequency of Typical and Atypical infarcts with Their Rates of Death and Complications*

	Total		Expired		Complications	
Typical	315	87.7%	86	27.3%	101	32.0%
Atypical	44	12.3%	1	2.3%	1	2.3%
Total	359		87	24.2%	102	28.4%

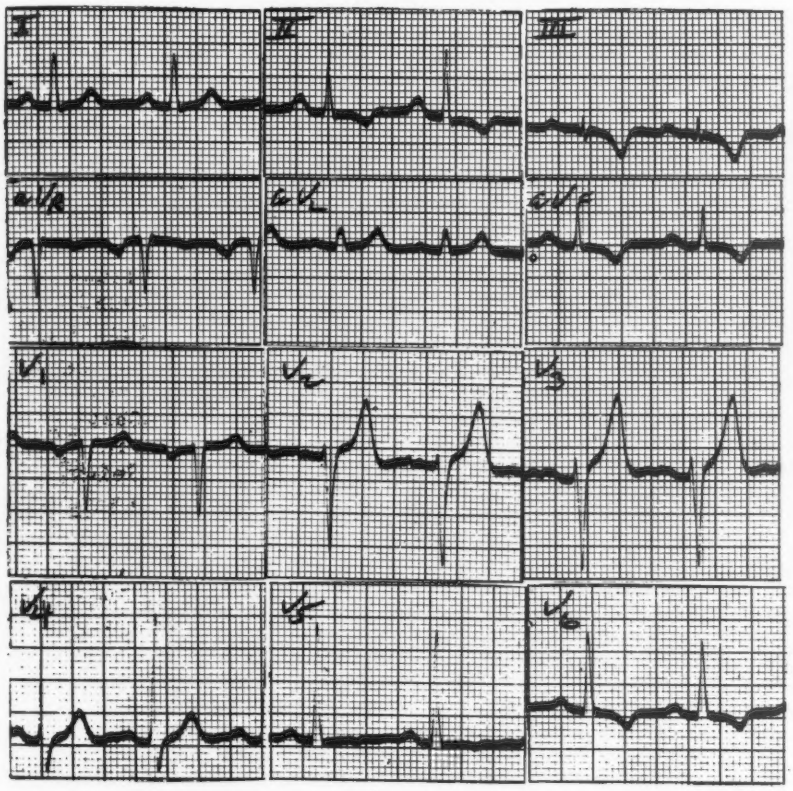

FIG. 3. Case 38. Electrocardiogram taken December 21, 1953. A tracing taken in 1957 was entirely normal.

She was readmitted to the hospital with severe congestive heart failure during June 1952. At that time she had slight pain suggesting coronary insufficiency.

Later in 1952 she died suddenly during a severe attack of retrosternal pain.

Case 38. A 47-year-old white man was admitted to the hospital on December 4, 1953, following 24 hours of intermittent retrosternal distress. Examination showed normal findings except for a blood pressure of 160/110. His tracing taken upon admission showed slightly inverted T waves in leads III, aV_F, V_5, and V_6. His white cell count was 10,000 per mm.^{3} and his sedimentation rate was 33 mm. per hour; subsequent sedimentation rates were 19, 35, and 44 mm. per hour. He was afebrile throughout his hospital stay.

TABLE 3.—*Follow-up Date Concerning 33 Patients 5 to 10 Years after Atypical Infarction*

Living	19
Healthy	12
Angina	4
Subsequent typical infarction	3
Dead	14
Died of cardiac disease	6
Died of other causes	4
Cause of death unknown	4

TABLE 4.—*Incidence of Atypical Infarcts in Various Studies*

	Total	Atypical	
CLINICAL			
Papp and Smith	109	33	30.2%
Littmann and Barr	178	11	6.2%
Prinzmetal et al.	200	30	15.0%
ECG			
Cutts et al.	784	69	8.8%
Memorial Hospital	359	44	12.3%

Tracings taken on December 11 and 17 showed progression of the degree of T-wave inversion. One taken on December 21 (fig. 3) showed maximum T-wave inversion in leads II, III, aV_F, and V_6; the QRS complexes remained normal.

He was discharged improved, and at present is healthy. His tracing has returned to normal and he has had no recurrence of symptoms.

Results

The data are presented in table 1. Thirty-one patients showed changes in the precordial leads; 14 showed changes in leads II, III, and aV_F. The single atypical case to die was an elderly, obese, diabetic woman (case 19) who clinically would not be called atypical or mild. The single complication in an atypical case was a bout of transient atrial fibrillation.

Seven patients showed significant ST-segment elevation. Only 4 of the atypical cases showed a delay in the development of electrocardiographic abnormalities; 1 of these did not develop changes until 2 weeks after the episode of pain and muscle damage; of the others, 2 developed changes in 5 days and 1 in 1 week.

The results are summarized in table 2.

Of the 43 patients who survived the initial attack, follow-up data were obtained in 33 and these are summarized in table 3. The number of patients is too small to permit conclusions but the data suggest that the long-term prognosis may be more favorable than that following typical infarction.

Table 4 compares the incidence of atypical infarcts in this study with those from previous studies.

Summary

The small, atypical myocardial infarct is a clinical entity, and the electrocardiogram can be of great help in making this diagnosis. The immediate prognosis in this type of case is excellent.

Summario in Interlingua

Le micre, atypic infarcto myocardial es un entitate clinic. Le electrocardiogramma pote esser de grande adjuta in establir le diagnose. Le prognose immediate es excellente.

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It is greatly to be doubted, that angina pectoris has ever occurred in a patient perfectly free from organic disease of the heart or aorta; and it is more probable that, in the cases so described, the disease was overlooked, than that the heart was perfectly sound.—William Stokes. *The Diseases of the Heart and the Aorta.* Dublin. Hodges and Smith, 1854, p. 482.

Late Hemodynamic Complications of Anastomotic Surgery for Treatment of the Tetralogy of Fallot

By RICHARD S. ROSS, M.D., HELEN B. TAUSSIG, M.D., AND MELVIN H. EVANS, M.D.

Seventeen patients with late hemodynamic complications of anastomotic surgery for the tetralogy of Fallot have been studied. Two syndromes have been noted and both seem related to shunts of greater than ideal size. The clinical characteristics of these syndromes are delineated.

DEFICIENT pulmonary blood flow is the basic physiologic abnormality in the classical tetralogy of Fallot, since a large portion of the venous blood returned to the right heart is pumped out the aorta. Surgical anastomosis of a systemic artery to the pulmonary artery increases pulmonary blood flow and brings about great clinical improvement. The Blalock-Taussig operation, in which the end of the subclavian artery is anastomosed to the side of the pulmonary artery, and the Potts operation, in which an anastomosis is created between the aorta and pulmonary artery, have been employed extensively to accomplish this purpose.[1, 2] These operations, and also the anastomosis of the innominate artery to the pulmonary artery, create what is essentially an artificial ductus arteriosus. In contrast to the situation in a naturally occurring patent ductus arteriosus, the blood passing through this artificial ductus contains a substantial proportion of unoxygenated blood that has passed into the aorta from the right heart.

It has been recognized since the early years of anastomotic surgery that the communication must exceed a certain minimal size in order to achieve the desired improvement in cyanosis and exercise tolerance. An anastomosis of adequate size for a child may become too small as the patient becomes an adult[3] or the anastomosis may be partially or completely occluded by thrombosis.[4] The complications that result from an anastomosis which is too large are less frequent. The construction of a shunt of excessive size may result in immediate heart failure and death within a matter of days after operation. Prolonged observation of patients after operation reveal that other consequences of an excessively large anastomosis may appear after many years. The 3 patients to be presented illustrate such late complications of a systemic-pulmonary anastomosis that is too large.

Case 1. JHH #615031, A-90909

This white male was first seen at age 27 because of cyanosis and exertional dyspnea. He had been cyanotic since birth but felt that his exercise tolerance had improved with increasing age. There was a history of squatting in childhood. On physical examination there was cyanosis of the lips. The heart was not enlarged, the rhythm was regular, and a harsh systolic murmur was heard along the left sternal border. The lungs and abdomen were normal. The red blood cell count was 7.2 million per mm.^{3}, and the hematocrit was 65 per cent. The electrocardiogram showed right ventricular hypertrophy. Chest x-ray at the time of the first examination is shown on the left of figure 1. Rapid and simultaneous filling of the aorta and pulmonary artery was demonstrated by angiocardiography. The diagnosis of tetralogy of Fallot was established.

A 6.5-mm. Potts anastomosis was constructed between the aorta and the pulmonary artery and a continuous murmur was heard postoperatively. During the first 14 months after operation the continuous murmur was noted to have decreased in intensity and it was not heard after the twenty-

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FIG. 1. Chest x-rays, case 1. *Left*, 7/17/52, preoperatively; *right*, 5/21/56, during terminal illness.

fourth postoperative month. As the murmur decreased, the hematocrit rose from 54 to 74 per cent and thrombosis of the anastomosis was suspected. Exercise tolerance decreased, cyanosis increased, and the patient noted frequent episodes of dyspnea and tachycardia.

Physical examination during the terminal illness 4 years after operation revealed cyanosis, minimal enlargement of the heart, a presystolic gallop rhythm at the apex, and no murmurs. The lungs were clear and the liver tender and enlarged to 5½ fingerbreadths below the costal margin. X-ray of the chest at this time (fig. 1, right) revealed a striking enlargement of the left pulmonary artery that had not been present immediately postoperatively. No pulsation was visible in the artery on fluoroscopy. A cardiac catheter was passed from the right ventricle into the aorta, but the pulmonary artery was not entered. The pressure was essentially the same in the right ventricle and aorta and the oxygen saturation of the aortic blood was 58 per cent.

No further surgery was deemed advisable. A loss of 7 pounds followed treatment with digitalis and thiomerin. The patient was discharged home but returned within 1 month because of increasing dyspnea and cyanosis. The physical findings were essentially unchanged. The patient became apprehensive and increasingly dyspneic and died suddenly on the night of admission.

At autopsy there was valvular and infundibular pulmonary stenosis associated with a ventricular septal defect and overriding of the aorta. The Potts anastomosis was seen to be widely patent (fig. 2), measuring 12 mm. in diameter as opposed to 6.5 mm. measured at operation. In the main pulmonary artery there was gross atherosclerosis, which was more extensive than in the adjacent aorta (fig. 2). Microscopic examination of the lungs revealed extensive changes in the small pulmonary arteries (fig. 3). Some vessels showed concentric narrowing and others showed areas of intimal thickening and occlusion with recanalization.

Comment. Although the pulmonary artery pressure was not obtainable, it is reasonable to assume from the clinical findings and examination of the pulmonary vesssels that pulmonary hypertension had developed prior to death. Presumably, a rise in pulmonary resistance occurred, the pulmonary artery pressure rose, the pulmonary artery dilated, and the anastomosis enlarged. As the pulmonary pressure approached that in the aorta the flow through the anastomosis diminished to such an extent that the anastomotic murmur disappeared. Thus, the patient was physiologically deprived of the anastomosis even though anatomically it remained open. The decrease in pulmonary blood flow was followed by a return of cyanosis and a rise in hematocrit.

Case 2. JHH #A-41658

The second patient differs significantly from the first in that 10 years elapsed between operation and the appearance of complications. This patient was first seen as a boy of 6½ years and had been cyanotic since early infancy. His activity was

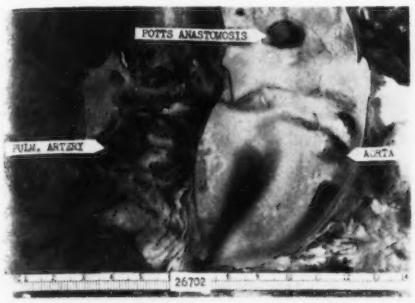

FIG. 2. Aorta and pulmonary artery, case 1. Potts anastomosis open. Gross atherosclerosis of pulmonary artery adjacent to anastomosis.

limited by dyspnea on slight exertion, but he had been attending school. On physical examination he was found to be cyanotic and there was slight clubbing of the fingers and toes. There was a faint systolic murmur at the base of the heart. The hematocrit was 81 per cent, the red cell count 9.7 million per mm.,^{3} the arterial oxygen saturation 61 per cent.

At operation Dr. Alfred Blalock found the innominate, carotid, and subclavian arteries to be of unusually large size. The right subclavian was larger than the right pulmonary artery, but a satisfactory end-to-side anastomosis was constructed between these 2 vessels. The postoperative course was complicated by recurrent hemorrhagic pleural effusions. In the immediate postoperative period the erythrocyte count fell to 6.7 million per mm.^{3} and the arterial oxygen saturation rose to 81 per cent. Two years after operation the erythrocyte count was 5.5 million per mm.^{3} and the oxygen saturation was 83.2 per cent. The patient complained of dyspnea only on vigorous exertion.

Five years after operation the patient was leading an essentially normal life but avoided competitive athletics. The chest x-ray taken during the fifth postoperative year is seen on the left in figure 4. At this time the pulmonary vascular markings were prominent.

Ten years after operation, at age 16, he was able to carry on normal activities without fatigue and could climb 2 flights of stairs easily. In addition to the continuous murmur of the anastomosis, which had been heard since operation, the patient developed a blowing, high-pitched descrescendo early diastolic murmur in the second and third left interspaces. The erythrocyte count was 6.47 million per mm.^{3} On x-ray both pulmonary arteries were prominent.

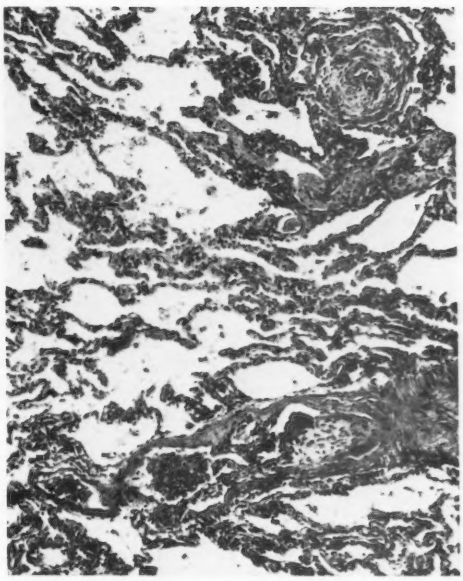

FIG. 3. Microscopic section of lung from case 1. Vessel at top shows concentric narrowing. Vessel at bottom, cut tangentially, shows intimal proliferation.

Eleven years after operation the patient reported several episodes of hemoptysis. On one occasion one half cup of blood was expectorated and on numerous occasions the sputum was blood-streaked. His exercise tolerance was essentially unchanged. The basal diastolic murmur was heard, as was the continuous murmur of the anastomosis. On fluoroscopy the pulmonary conus was prominent and the left pulmonary artery was described as huge ("the size of an orange"). Chest x-ray at this time is shown at the right of figure 4. The massively dilated pulmonary artery filled on angiocardiography, proving that it was not an extravascular shadow (fig. 5). Cardiac catheterization demonstrated the presence of a ventricular septal defect, but unfortunately the pulmonary artery was not entered.

Figure 6 shows the changes in hematocrit and pulmonary artery size during the 11 years following operation. It can be seen that the immediate response was excellent, with a fall in hematocrit that was accompanied by clinical improvement in color and exercise tolerance. The line diagrams at the top of the figure are tracings of the left heart border showing the progressive enlargement of the left pulmonary artery. The mean frontal plane area of the heart increased during the last several years from 122 cm.^{2} to 166 cm.^{2}

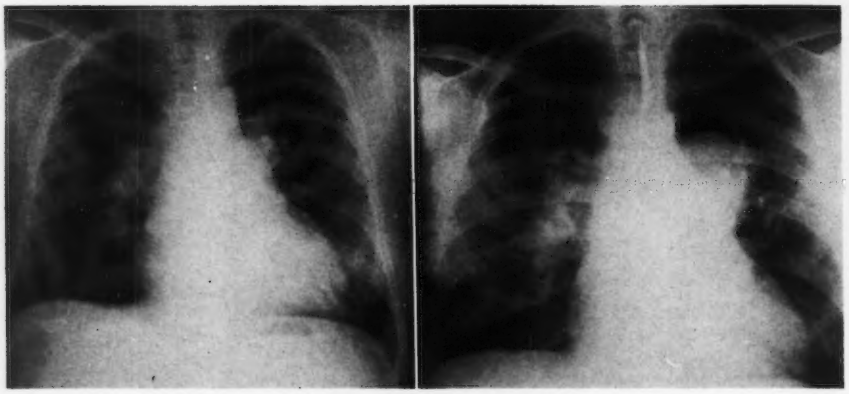

FIG. 4. Chest x-rays, case 2. *Left*, 1/28/50, 5 years after operation; *right*, 3/17/56, 11 years after operation.

The patient died suddenly during the twelfth postoperative year and autopsy was performed at the Maimonides Hospital of Brooklyn, New York.* Postmortem examination confirmed the original diagnosis of ventricular septal defect and pulmonary stenosis. The pulmonic valve was "completely atretic" and showed "no stoma of communication between the ventricle and the huge pulmonary artery." Infundibular stenosis was also present. There was a ventricular septal defect measuring 2.5 cm. in diameter immediately beneath the overriding aorta.

The main pulmonary artery measured 7 cm. in diameter, as did the primary branches in their maximum dimension. The subclavian-pulmonary anastomosis was open, measuring 2.5 cm. in diameter. There was an aneurysmal sac on the left wall of the main pulmonary artery measuring 4 cm. in average diameter from which a dissecting aneurysm of the pulmonary artery originated. This dissecting aneurysm, measuring 3 cm. in length, extended from a break in the intima 4 cm. distal to the pulmonary valve to an area on the outer surface of the pulmonary artery from which blood leaked on pressure. This area was within the pericardium and was apparently responsible for the 300 ml. of blood found in the pericardium. Extensive intimal fibrosis was present in both medium and small pulmonary arteries.

Comment. This man had many features in common with the previous patient. It is probable that he, too, had pulmonary hypertension secondary to pulmonary vascular changes. The continuous murmur was present at the time of his last examination and the anastomosis was open at autopsy, but the rising hematocrit indicated that the volume of the shunt was decreasing.

Case 3: JHH #B-16505

This patient exhibited congestive heart failure and cardiac enlargement, but did not have the striking pulmonary artery enlargement seen in the first 2 patients. This syndrome, which is physiologically distinct from that exhibited by the first 2 patients, appears to be another consequence of a shunt of excessive size.

This patient was first seen at age 23 with a history of cyanosis since birth, diminished cardiac reserve during infancy and gradual improvement during adolescence. Physical examination, laboratory and x-ray studies, confirmed the diagnosis of tetralogy of Fallot. The preoperative chest film is seen at the left of figure 7.

A 7-mm. Potts anastomosis was created between the aorta and pulmonary artery in 1955. Following operation the hematocrit fell from 74 to 49 per cent and the patient was pleased with his symptomatic improvement. One year after operation the transverse diameter of the heart had increased to 60 per cent of the thoracic diameter (figure 7, right), as opposed to a preoperative value of 50 per cent (fig. 7, left).

*The authors wish to thank Dr. Max Palinsky of Brooklyn, N. Y., who attended the patient during his terminal illness, and Dr. Abraham Kantrowitz and Dr. Abdul Naji, who conducted the pathologic examination for making the pathologic findings available.

FIG. 5. Angiocardiogram, case 2, showing massive main pulmonary artery filled with radiopaque material.

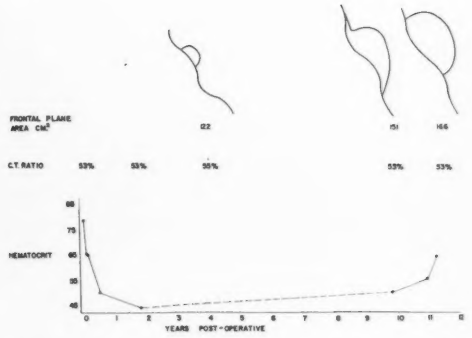

FIG. 6. Case 2. *Line diagrams,* top of chart, tracings of left heart border showing progressive enlargement of pulmonary artery. Mean frontal plane area of heart, calculated by method of Hodges and Schwarz, is recorded. Peripheral venous hematocrit plotted against time, bottom of chart.

Two years after operation the patient complained of epigastric fullness and his liver was found to be enlarged. Five pounds of weight were lost following an injection of a mercurial diuretic. Diuretics and digitalis were required to control abdominal distention and breathlessness. On physical examination there was no cyanosis, a collapsing pulse was seen in the neck, the blood pressure was 168/75 mm. Hg in the right arm, and pistol shot sounds were heard over the femoral arteries. There was a forceful apical impulse with a sustained heave. A loud continuous murmur was heard over the entire chest. The chest x-ray (fig. 7) revealed a cardiothoracic ratio of 60 per cent, but the pulmonary artery was not unusually dilated. The electrocardiogram showed more evidence of left ventricular hypertrophy than had been seen in the preoperative records. Pulmonary pressure was 40/22 mm. Hg at cardiac catheterization, 28 months after operation. A large pulmonary blood flow was indicated by the oxygen saturation of 95 per cent in the pulmonary arteries.

Comment. The primary problem here appears to be excessive left ventricular work leading to cardiac enlargement and congestive failure. The physical findings in this third patient suggested that the physiologic prob-

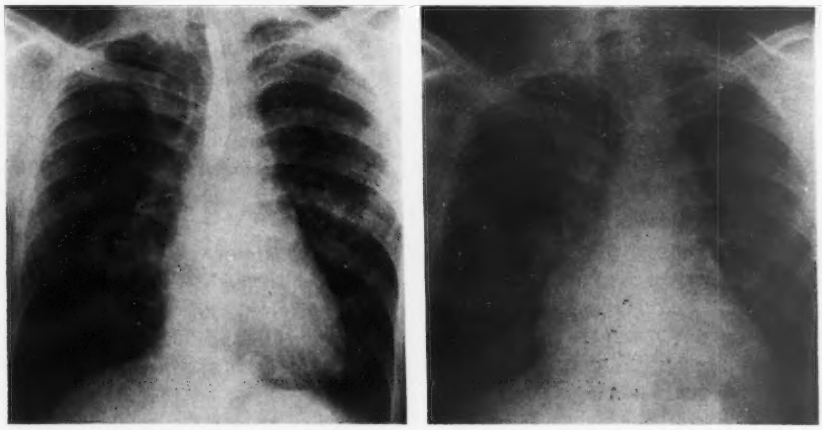

FIG. 7. Chest x-rays of case 3. *Left,* 1/3/55, preoperative; *right,* 4/5/57, 1 year after operation.

TABLE 1.—*Seventeen Patients with Late Hemodynamic Complications after Surgery*

Patient	Age at operation	Operation	Current Status: Age	Cardiothoracic ratio (%)	Pulmonary artery enlargement	Congestive failure	Systemic B.P. mm. Hg
1	27	6.5-mm. Potts	31	68	+	+	100/64
2	7	R B-T	19	54	+		130/70
3	23	7-mm. Potts	25	60		+	168/75
4	10	R B-T	20	62	+		110/64
5	13	R I	22	65	+		120/70
6	3	L B-T	6	62	+		126/80
7	7	L B-T	10	50	+		105/60
8	13	L & R B-T	20	59	+		190/65
9	11	L I	24	50	+		
10	13	6.5-mm. Potts	22	65			136/0
11	7	R B-T	18	65			112/80
12	19	L B-T	29	70			131/48
13	7	L B-T	16	65			120/70
14	13	5-mm. Potts	16	62			120/70
15	9	R B-T	18	67			110/58
16	12	R B-T	17	65			106/45
17	11	L B-T	15	62			100/50

Potts anastomosis constructed between aorta and pulmonary artery.

R B-T, right Blalock-Taussig anastomosis; right subclavian to right pulmonary artery anastomosis.

L B-T, left Blalock-Taussig anastomosis; left subclavian to left pulmonary artery anastomosis.

R I, right innominate to right pulmonary artery anastomosis.

L I, left innominate to left pulmonary artery anastomosis.

lem is similar to that in patients with large arteriovenous fistulae. The wide pulse pressure and collapsing pulses reflect the large volume of blood flowing from the aorta to the pulmonary circulation. The situation is not exactly comparable to that in patients with arteriovenous fistulae in that in this patient the shunt was created to compensate for a malformation that is still present. The pulmonary stenosis and ventricular septal defect remain, and therefore right ventricular pressure and work are still increased above normal values.

Seventeen patients similar to the 3 presented above have come to our attention and are listed in table 1. There are 8 patients (cases 1, 2, 4–9) with pulmonary artery enlargement of the degree noted in patients 1 and 2. Patients 1 and 2 are the only ones in whom the hematocrit has risen and cyanosis returned. It seems likely that the other 6 patients also have pulmonary hypertension, which has reduced the volume of the shunt, but that the critical level at which cyanosis and polycythemia return has not been reached. Only 2 patients have shown signs of congestive heart failure (patients 1 and 3). Patient 10 is similar to patient 3 in that cardiac enlargement and a wide arterial pulse pressure exist, but patient 10 has shown no signs of congestive heart failure. Progressive increase in heart size is the only indication that the shunt is too large in patients 10 through 17. No meaningful estimate of the incidence of these complications can be made prior to the completion of the survey of all patients who have survived 10 years after operation.

DISCUSSION

There is probably a precise relationship between the severity of the original malformation in patients with the tetralogy of Fallot and the magnitude of the shunt necessary for optimal physiologic compensation. If the shunt is smaller than this optimal value and the pulmonary blood flow is not restored to normal levels, cyanosis will not be completely alleviated. If, on the other hand, the shunt is larger than this theoretical optimal value, the cyanosis will disappear and the patient will have an excellent initial result, but late complications may develop. There appear to be 2 physiologic sequences that may follow the creation of too large an anastomotic pathway.

First, part of the left ventricular output is directed through the anastomosis to the pulmonary circulation. Systemic flow must be maintained, and hence the left ventricular output and work must of necessity increase. If this work load exceeds the ability of the ventricular muscle to respond, congestive failure results. In this regard it is possible that either congenital or developmental le-

ficiencies of the myocardium may play a significant role. This sequence of events might be referred to as the arteriovenous fistula failure syndrome. Tachycardia, systolic hypertension, wide pulse pressure, cardiac enlargement, venous hypertension, hepatomegaly, and fluid retention are the salient features of this syndrome. Such was the clinical picture in the third patient.

Second, if pulmonary hypertension develops either due to pre-existing thrombotic occlusions or changes that are secondary to increased flow or pressure, a different physiologic sequence is seen. Pulmonary resistance increases, flow through the anastomosis decreases and, hence, the left ventricular work load is lessened. Thus, pulmonary hypertension might conceivably be considered to offer protection against the arteriovenous fistula failure syndrome. As pulmonary pressure rises, the pressure gradient between the systemic and pulmonary terminals of the anastomosis decreases; as these pressures approach equality, the flow through the anastomosis may cease. Pulmonary stenosis and right ventricular hypertension persist and right ventricular failure may develop, as in patient 1. As the volume of the shunt lessens, arterial oxygen saturation decreases, and polycythemia and cyanosis return. The clinical manifestations of this pulmonary hypertension syndrome are enlargement of the pulmonary artery on x-ray, diminution in intensity of the anastomotic murmur, rising hematocrit, increasing cyanosis, and possibly cough and hemoptysis.

We were not able to record pulmonary artery pressures in either patient 1 or patient 2. The clinical history and the microscopic examination of the lungs constitute the evidence upon which we base the diagnosis of pulmonary hypertension. Pulmonary hypertension has been documented in a similar patient to be reported by Rapaport and Leeds.[5] Elevated pulmonary artery pressure was recorded at thoracotomy in a 46-year-old woman 8 years after a Blalock-Taussig anastomosis.

There are 2 plausible explanations for the pulmonary vascular changes responsible for the increase in pulmonary resistance. First, it is possible that these organized occluded vessels existed prior to operation. Similar changes were described in 1948 by Dr. Arnold Rich[6] in patients with the tetralogy of Fallot who died prior to surgery. The development of pulmonary hypertension after operation might well be related to the extent of the preoperative damage to the pulmonary vasculature. An alternative explanation fits better with the clinical facts in the second patient, who developed pulmonary hypertension 10 years after operation. In this patient it seems likely that the vascular changes developed as a consequence of operation and were related to the increased pulmonary blood flow or pressure, as in other conditions characterized by a left-to-right shunt.

The pathogenesis of the pulmonary hypertension that develops in patients with congenital heart disease and increased pulmonary blood flow is not completely understood. A careful study of pulmonary vascular changes in patients who died after anastomotic operations would be a useful addition to currently available information regarding pulmonary hypertension in these circumstances. Such a study is currently in progress at The John Hopkins Hospital.

Two less likely explanations for the pulmonary vascular changes deserve consideration. It is theoretically possible that areas of stenosis in the pulmonary arteries distal to the anastomosis could be responsible for pulmonary hypertension, but the sequence of early improvement followed by evidence of decreasing shunt could not be explained on this basis. It is also possible that multiple small emboli from the anastomosis could have produced the pulmonary vascular changes, but there was no evidence of thrombus formation on the Potts anastomosis in the first patient.

The last 7 patients in table 1 are included only because of increasing heart size; all are asymptomatic. We suspect that they represent an earlier or less severe stage of the syndrome exhibited by the third patient. The heart size usually increases slightly during the first year after operation in patients with

a satisfactory postoperative course. The increase in size is to be expected because of the increased left ventricular work and also because of the patient's increase in physical activity. The heart size usually becomes stable after 1 year in those patients whose shunt is presumably of optimal size. Progressive increase in heart size beyond the first year in a patient with the tetralogy of Fallot is strong presumptive evidence of too large a shunt.

Consideration of the change in heart size may be useful clinically in the differentiation of a reduction in the shunt due to anatomic closure and a reduction in the shunt due to pulmonary hypertension. If cyanosis returns and the heart size remains small, it is likely that the anastomosis has closed anatomically. If, on the other hand, progressive enlargement of the heart precedes the return of cyanosis, the development of too large a shunt would appear more likely.

Eleven patients in this group of seventeen had end-to-end subclavian to pulmonary anastomoses. In 2 the innominate artery was used, and in 4 an aorta to pulmonary anastomosis was constructed. Thus, the larger anastomoses constitute more than one third of the patients in this group, representing a much higher frequency than in the entire operated population. It appears obvious, therefore, that these complications are more frequent with larger anastomoses. It should be stated in this regard that the Potts anastomoses in 3 of the 4 patients were larger than the usually recommended size, i.e., 6.5, 6.5, and 7 mm. in diameter. It is also worthy of emphasis that the anastomosis in the first patient increased in size from 6.5 to 12 mm. during the 4 years after operation. Increase in size of an anastomosis of smaller initial dimensions has not been proved but might conceivably occur. The greater length of the limiting lumen of a subclavian-pulmonary anastomosis makes it less likely that such an anastomosis would increase in size.

We have no experience with surgical therapy to alleviate these complications in the group discussed, all of whom have had the classic tetralogy of Fallot, but a situation that is physiologically indentical has been treated. A clinical picture similar to that presented by case 3, with cardiac enlargement, hepatic enlargement, and fluid retention, was seen in a 19-year-old boy with pulmonary stenosis and a single ventricle who had an 8-mm. Potts anastomosis. One year after the initial operation the Potts anastomosis was taken down and a left end-to-side subclavian to pulmonary anastomosis constructed. At the time of operation the Potts anastomosis was estimated to be 10 to 12 mm. in diameter. One year after the second operation the heart was still large but exercise tolerance had increased and heart failure was more easily controlled. Obviously, open heart correction of the primary malformation would be the treatment of choice for these complications but was not considered possible in the above-mentioned patient because of the single ventricle. The third case presented is considered a possible candidate for surgical correction of the primary malformation by means of open heart technic.

Summary

Two syndromes may develop as late hemodynamic complications of anastomotic operations for the tetralogy of Fallot. Both can be related to a shunt of greater than ideal size. The first is characterized by cardiac enlargement and congestive failure similar to that seen in patients with arteriovenous fistulae. The second is characterized by pulmonary hypertension, aneurysmal dilatation of the pulmonary artery, decreasing shunt, return of cyanosis, cardiac failure, and death.

Summario in Interlingua

Duo syndromes occurre como tardive complicationes de chirurgia anastomotic in casos del tetralogia de Fallot. Ambes pote esser relationate a un derivation de dimensiones plus que ideal. Le prime es characterisate per allargamento cardiac e disfallimento congestive simile a illo vidite in patientes con fistulas arteriovenose. Le secunde es characterisate per hypertension pulmonar, dilatation

neurysmal del arteria pulmonar, decrescen-
a, del derivation retorno de cyanose, disfalli-
ento cardiac, e morte.

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Campbell, M., Neill, C., and Suzman, S.: The Prognosis of Atrial Septal Defect. Brit. M. J. **1**: 1375 (June 15), 1957.

The physical signs, radiologic findings, electrocardiographic changes and differential diagnosis of atrial septal defects are discussed and various clinical and catheterization data are presented for 100 patients studied by the authors. Of this group the diagnosis was proved by catheterization or necropsy in 66 patients, including 7 with anomalous pulmonary venous drainage and 8 others with pulmonary valvular stenosis in addition. In the other 34 patients the diagnosis seemed certain on clinical grounds. Observation of the course of these patients indicates that after infancy is passed the first 2 decades are relatively normal periods, but the prognosis in the fourth and fifth decades is much less good and only one half of these seen at the hospital are still well at 40 and less than a quarter at 50. Usually the heart is large, often of such size as would generally indicate a poor prognosis, but nearly all patients who survive the first year or so do well without the heart becoming any larger until 25 and more often 35 years of age. Then, in an increasing number, but not in all, the strain of the large right ventricular output produces increasing dyspnea and ultimately right-sided heart failure. In some patients pulmonary arterial pressure rises, reversing the shunt and producing central cyanosis and pulmonary artery thrombosis.

Sagall

A Reversible Nephrotic Syndrome Associated with Congestive Heart Failure

By W. Richard Burack, M.D., Jack Pryce, M.B., B.S., and John F. Goodwin, M.D., F.R.C.P.

Attention is drawn to the occurrence of the nephrotic syndrome during chronic heart failure and to its reversibility over a period of months on a regimen of digitalis, low-salt diet, and weekly, parenterally administered, mercurial diuretics. It is therefore concluded that the nephrotic syndrome was not caused by mercurial diuretics and is not a contraindication to their use. Reference is made to the poorly understood phenomenon of proteinuria in heart failure and its possible relationship to these cases.

A NEPHROTIC syndrome is an unusual and puzzling complication of chronic heart failure about which very little has been written. The object of this communication is to record and to discuss 4 instances in which severe proteinuria, hypoproteinemia, massive edema, hypercholesterolemia, and a strikingly abnormal plasma electrophoretic pattern developed in the course of congestive heart failure and to emphasize the reversibility of the process.

Four similar patients were reported by Munck and Nissen.[1] With the exception of 1 patient who died and came to autopsy, their subsequent courses were not described.

Biochemical Methods

Serum albumin, cholesterol, and urea were estimated according to the method of King and Wootten.[2] Protein concentration in pooled 24-hour urine collections was estimated by the method of Esbach.[3]

Case Reports

Case 1. (H. H., no. 165634). A 50-year-old man was admitted in October 1954 because of paroxysmal and exertional dyspnea and wheezing. Blood pressure was 220/120 mm. Hg, and jugular venous pressure 5 cm. above the sternal angle. There were a soft apical pansystolic murmur, a presystolic triple rhythm, bilateral basal rales, and electrocardiographic evidence of left ventricular hypertrophy. Urinalysis, including microscopic examination of sediment and test for protein, was normal. An intravenous pyelogram was normal, and the kidneys could concentrate urine to a specific gravity of 1.021.

The patient was discharged on digitalis, reserpine, ammonium chloride, and 3 tablets daily of chlormerodrin, an oral mercurial diuretic. In December 1954, he was readmitted for better control of the hypertension. This time the urine had a trace of protein. By means of pentolinium, the blood pressure was satisfactorily lowered to 140/90 mm. Hg recumbent and 115/75 mm. Hg standing. He was given several injections of mersalyl, but because of some scaliness of the skin, it was discontinued. The blood urea was 29 mg. per cent.

In March 1955, the patient was readmitted with a severe acute posterior myocardial infarction with left ventricular failure, and he was given mersalyl by injection, with a good diuresis and weight loss. Nevertheless he began to accumulate sacral edema and by the end of the second hospital week had a proteinuria of 3 to 4 Gm. per day. The urine specific gravity reached 1.025 after 24 hours' dehydration, and the urea clearance was normal. Seventy per cent of an injected test dose of Congo red was still in the blood after 1 hour. The infarction evolved in the usual way, and he continued to receive a weekly 2-ml. injection of mersalyl. At the time of discharge in April 1955, there was some ankle edema, the total serum protein was 6.2 Gm. per cent, and there was a proteinuria of 3 to 4 Gm. per 24 hours. Digoxin and weekly mersalyl were continued on an out-patient basis. He felt well, but in February 1956 was readmitted because the edema and proteinuria persisted. The blood pressure was 190/100 mm. Hg and there were rales at the lung bases as well as massive dependent edema. The urine showed a few hyaline casts and contained 9 Gm. of protein per 24 hours. No organisms grew from a urine culture. The blood urea was 37 mg. per cent. The blood cho-

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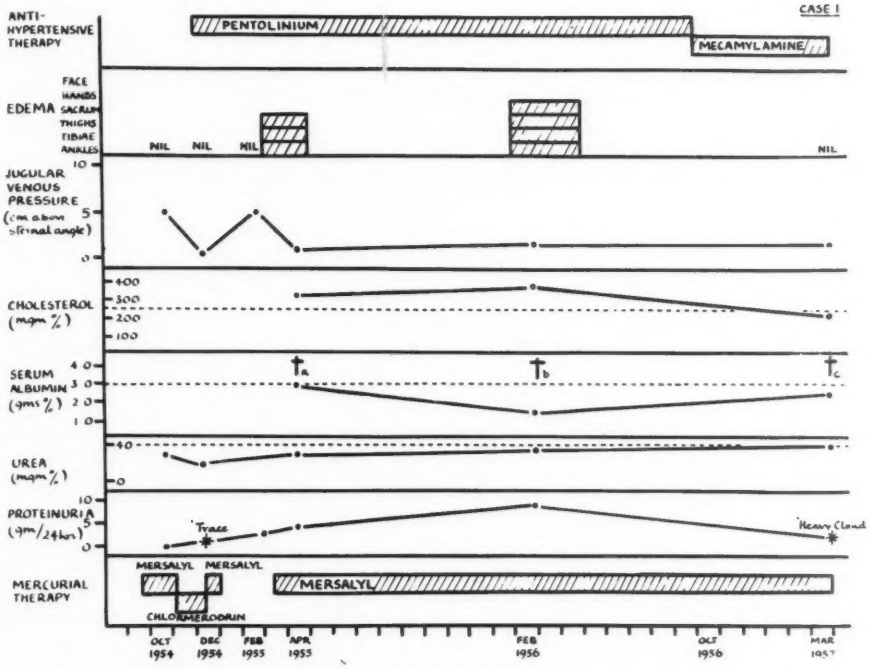

FIG. 1. Progress chart of case 1. *Results of qualitative test (sulfosalicylic acid) on single voided specimens and estimated level of 24-hour excretion. †Times corresponding to electrophoretic patterns in figure 2. *Dotted lines,* normal level (approximately).

lesterol was now 377 mg. per cent, and the total serum protein 5.5 Gm. per cent with 1.3 Gm. per cent albumin. Another Congo red test was normal. Renal biopsy showed "a patchy thickening of the capillary basement membranes," a finding that is not uncommon in congestive heart failure. Retrograde inferior caval venography showed no inferior vena caval or renal vein obstruction. The urea clearance was 100 per cent of normal. Cortisone was without effect on the proteinuria. Throughout his stay he received periodic mersalyl injections, and when he was discharged in April 1956, he had begun to have a small diuresis with each of them. From this time he has been seen in the out-patient department, where, in March 1957, he was feeling well and was without edema of the ankles. He was still taking a weekly injection of mersalyl in addition to digoxin, ammonium chloride, and a low-salt diet. Mecamylamine was substituted for pentolinium. His blood pressure was 150/90 mm. Hg, blood urea 42 mg. per cent, blood electrolytes all normal, cholesterol 220 mg. per cent, and serum albumin 2.4 Gm. per cent. The albumin/globulin ratio was still reversed, however, and a qualitative sulfosalicylic acid test for urine protein revealed a heavy cloud. He has been back at regular work for 1 year (figs. 1 and 2).

Case 2. (H. H., no. 161211). A 43-year-old woman, with symptomatic mitral valve disease and atrial fibrillation for 13 years, had, for the last 3 years of her life, evident tricuspid incompetence with a pulsating liver and mild jaundice. From April 1954, at which time her urine was free of protein, she received either a weekly 2-ml. injection of mersalyl or 2 daily tablets of an oral mercurial diuretic (chlormerodrin) in addition to digitalis and a low-salt diet. In November 1955, she was free of edema and doing well, but in January 1956 her dyspnea and ankle edema increased. In May 1956, she was admitted to the hospital with grossly edematous legs and sacrum and bilateral basal rales. The jugular venous pressure was 10 cm. above the sternal angle, with a pronounced systolic pulsation. Urine protein excretion varied from 3 to 10 Gm. a day. No organisms grew from urine culture. The total

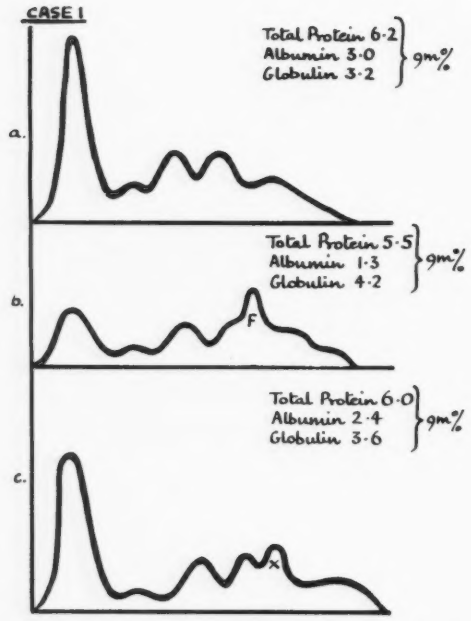

FIG. 2. Electrophoretic patterns of plasma proteins in case 1. *a*. Serum electrophoretic pattern early in the nephrotic syndrome. *b*. Pattern at the height of the syndrome. Plasma was used so that a fibrinogen peak, *F*, is evident. *c*. Protein pattern less abnormal. Significance of peak, *X*, is not clear.

serum proteins were 5.5 Gm. per cent with albumin 2.2 Gm. per cent. Serum cholesterol was 683 mg. per cent. Serum electrolytes and blood urea were normal. Eighty-two per cent of an injected test dose of Congo red was still in the plasma after 1 hour. An intravenous pyelogram was normal. Mercurial administration was discontinued and 8 weeks later there were 395 μg. of mercury in a 24-hour collection of urine. A course of dimercaprol was administered, and 7 days later there were still 315 μg. of mercury in the urine per 24 hours. Edema continued to accumulate, and therefore, on the basis of experience with case 1, mercurial injections were given again. This time she was given mercaptomerin in 2-ml. weekly, subcutaneous injections, and after each injection she had a small diuresis. Edema began to lessen, and by August 1956, the urine contained only 2 Gm. protein per 24 hours. She was therefore discharged from the hospital and remained at home as a semi-invalid (her exercise tolerance being severely restricted), receiving maintenance digitalis, a low-salt diet, ammonium and potassium chloride supplements, and twice weekly injections of mercaptomerin. In January 1957, there was only a moderate degree of pretibial edema and a faint trace of urinary protein by qualitative test. In March 1957 edema had disappeared, and many repeated qualitative tests for urine protein were negative. She continued to receive mercaptomerin up to and during her last admission to the hospital in March 1957, when her cardiac status suddenly deteriorated and she died. At postmortem examination, organic disease of the mitral valve was found with predominant incompetence and functional dilatation of the tricuspid valve ring without evident organic involvement. There was no evidence of old or recent thrombus in renal or inferior vena caval vessels, and histologic examination of the kidneys revealed only some protein material in a few tubules (figs. 3 and 4).

Case 3. (H. H., no. 189473). A 53-year-old woman had proteinuria, ankle edema, and hypertension with her last 2 pregnancies at the ages of 33 and 37, respectively, and was known to be hypertensive thereafter. At age 49 her blood pressure was 240/150 mm. Hg, and because of some dyspnea and ankle edema, she was given digitalis and 1 or 2 injections of mersalyl. Her blood urea was 39 mg. per cent. At age 50, because of recurrence of dyspnea and edema and blurring of vision, she was treated with hexamethonium and weekly injections of mersalyl, and for 2 years her symptoms and signs remained minimal. At age 52 dyspnea and edema returned, and she was admitted to her local hospital. Blood pressure was 220/130 mm. Hg, and pentolinium and reserpine were substituted for hexamethonium. The blood pressure fell to 140/80 mm. Hg, but at the same time edema continued to accumulate, and it was found that the pressure stayed at 140/80 mm. Hg even when pentolinium and reserpine were stopped. Mercurial injections now had no diuretic effect. Gross proteinuria developed, but the blood urea remained at 22 mg. per cent. She was discharged from the hospital because she felt well in spite of the extensive edema, and, while at home, she continued to receive weekly mersalyl injections and digitalis. Nevertheless, the edema increased and began to involve her thighs, and she was therefore readmitted to her local hospital. The blood pressure was 130/85 mm. Hg, blood urea 20 mg. per cent, serum albumin 2.4 Gm. per cent, and globulin 5.5 Gm. per cent. Cholesterol was 450 mg. per cent. A diagnosis of "mercurial nephrosis" was made and mersalyl was discontinued. With Southey tubes 58 pints of edema fluid were removed over an 8-month period in the hospital, during which infusions of Dextran and courses of dimercaprol, corticotropin, and cortisone were without effect. The blood urea was

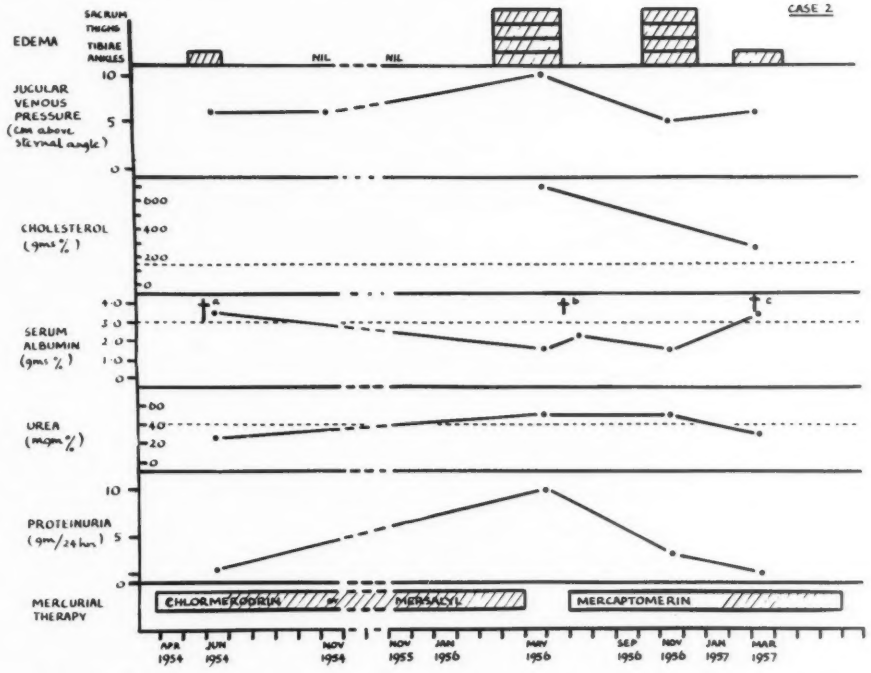

FIG. 3. Progress chart of case 2. †Times corresponding to electrophoretic patterns in figure 4. *Dotted lines,* normal level (approximately).

always within normal limits except on 1 occasion when it was 67 mg. per cent.

In August 1956, at a time when even her hands and face were becoming puffy, she was transferred to Hammersmith Hospital. On admission blood pressure was 210/120 mm. Hg and there was controlled atrial fibrillation. The left ventricle was enlarged, and there was a third sound at the apex. Jugular venous pressure was 10 cm. above the sternal angle with a systolic pulsation indicating tricuspid incompetence. Twenty-four-hour urine collections contained 9 Gm. protein, the blood cholesterol was 600 mg. per cent, serum albumin 1.1 Gm. per cent, and globulin 2.9 Gm. per cent. Daily urine volumes averaged 1500 ml., serum electrolytes were normal, urinary sediment was normal, and urine cultures were sterile. An insignificant amount of mercury was excreted per 24 hours (70 μg.). A Congo red test gave a negative result. Regular, twice weekly, intramuscular injections of mersalyl were started in the second week, and although at first without effect, it was found that when intravenous aminophylline was given at the same time, satisfactory diureses of 2,000 to 4,000 ml. resulted. On this form of treatment and with a diet containing 200 mg. of sodium and 200 Gm. of protein daily, her condition steadily improved. Edema lessened, and weight fell from 79.1 Kg. shortly after admission to 63.6 Kg. when she was discharged nearly 3 months later. Toward the latter part of her stay, mersalyl alone, without aminophylline, was again causing satisfactory diuresis. Weekly mersalyl injections, digitalis, and low-salt diet with high-protein supplements were therefore continued at home, and 4 months later in March 1957, when she was readmitted to Hammersmith Hospital for re-evaluation, edema was absent, the urine contained only 2 Gm. protein per 24 hours, and the blood cholesterol had fallen to 265 mg. per cent. The serum albumin was still only 1.7 Gm. per cent. Globulin was 3.4 Gm. per cent. Electrolytes were all normal. Chromatography of the urine revealed no abnormal aminoaciduria. By May 1957, the blood cholesterol was 242 mg. per cent, and the serum albumin 3.3 Gm. per cent, with globulin 2.5 Gm. per cent. A retrograde inferior vena caval angiogram showed no obstruction of the inferior vena cava or of the renal veins. She felt well and had only moderate dyspnea on exertion (figs. 5 and 6).

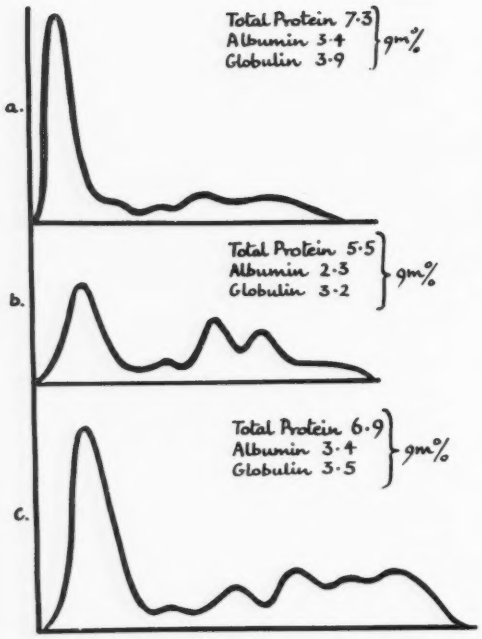

FIG. 4. Electrophoretic patterns of plasma proteins in case 2. *a*. An essentially normal pattern in 1954. *b*. At the height of the nephrotic syndrome in 1956. *c*. The improved pattern of March 1957.

Case 4. (H.H., no. 185083). A 70-year-old woman with an atrial septal defect had been receiving digitalis for heart failure since 1952. From late 1955 until January 1957, she had been receiving almost weekly parenteral mercurial diuretics. These were discontinued in January 1957 because of development of the nephrotic syndrome. In June 1957, she was passing up to 9 Gm. of protein in the urine each day, and the serum albumin was 2.1 Gm. per cent. The serum electrolytes remained normal, except for a slight but consistently elevated serum bicarbonate, and the blood urea never rose above 45 mg. per cent. The serum cholesterol rose from 212 mg. per cent in January 1957 to 357 mg. per cent in June 1957. No significant pyuria or microscopic hematuria had ever been evident.

After the mercurial diuretics were discontinued, the patient was treated with ion-exchange resins and a low-salt diet (1 Gm. of sodium chloride daily). Some improvement occurred, but she was readmitted to the hospital in September 1957 with extensive edema and jugular venous pressure 5 cm. above the sternal angle. Mercurial diuretics were now administered, but were without effect upon either the heart failure or nephrotic syndrome. The urine protein content varied from 1 to 6.9 Gm. per 24 hours, and the total serum proteins were 5.1 Gm. per cent (albumin 1.4, globulin 3.7). The serum cholesterol was 280 mg. per cent, and the blood urea 24 mg. per cent. She died suddenly in mid-October 1957, and at autopsy a large atrial septal defect was found. The pulmonary arteries were enormously dilated. The kidneys appeared congested but were otherwise normal, and microscopic examination revealed no definite abnormality. There was no evidence of a renal vein thrombosis.

DISCUSSION

Differential Diagnosis

The nephrotic syndrome may appear during the course of any of several disease conditions,[4, 5] most of which can be reasonably shown not to have been present in these 4 patients.

In adults the nephrotic syndrome may arise during the course of a primary renal disorder, but there is good reason to believe that none of these patients was suffering from pre-existing renal disease, because there was no azotemia, and cells were absent from the urine of all. In case 1, furthermore, renal biopsy failed to reveal any evidence of nephritis, and in cases 2 and 4 the kidneys were grossly and microscopically normal after death.

Secondary renal amyloid deposits are sometimes associated with the nephrotic syndrome, but in no instance was there a primary disease of the kind usually associated with secondary amyloidosis, and Congo red tests were negative. In cases 1, 2, and 4 no amyloid material was found in the kidneys.

We could find no evidence in any of our patients of "collagen" disease, another of the conditions known to be associated with the nephrotic syndrome. None was febrile, in case 1 a search for LE cells was negative, and in cases 2 and 4 "collagen" disease was excluded by the autopsy findings.

No evidence of recanalized thrombosis of the inferior vena cava or renal veins was found in the patients who came to autopsy, and retrograde venography eliminated any significant renal venous or caval block in the other 2.[6]

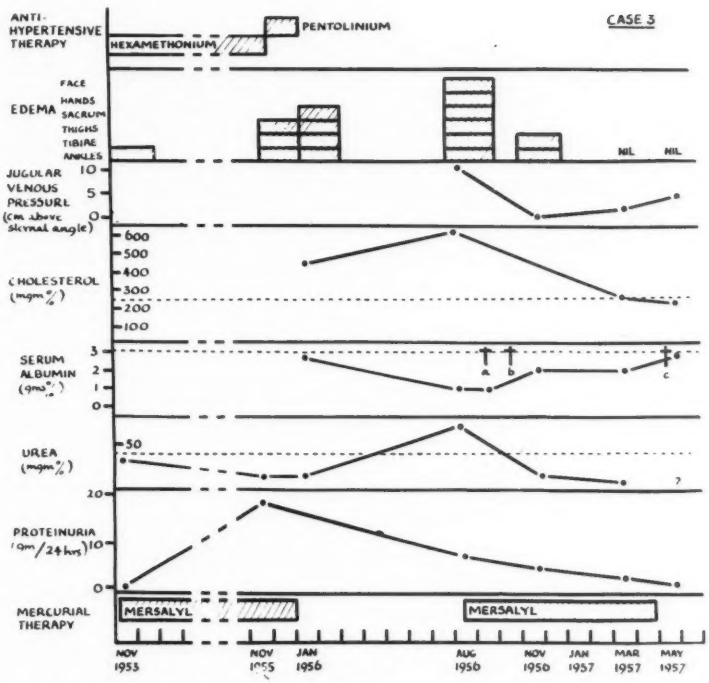

FIG. 5. Progress chart of case 3. †Times corresponding to electrophoretic patterns in figure 6. *Dotted lines,* normal level (approximately).

None of the cases was diabetic, and therefore Kimmelstiel-Wilson's intercapillary glomerulosclerosis does not enter into the differential diagnosis.

The Possible Role of Mercurial Toxicity

It may be asked whether the mercurial diuretics administered to these patients therapeutically could have had an adverse effect on kidney function.

Munck and Nissen,[1] who described 4 cases of nephrotic syndrome complicating heart failure, incriminated mercurial diuretics, although the kidneys of their patient who was autopsied (death from pulmonary embolus) showed "no definite changes" either grossly or microscopically. What is more, the authors were apparently unaware of the potential reversibility of the clinical picture, even in the face of continued mercurial diuretic administration.

Certain alleged instances of "toxic nephrosis" from mercurial diuretics[7, 8] seem in retrospect to have been instances of "low-salt syndrome" with a great deal of edema, and another in a patient who had received an oral mercurial diuretic lacks detailed documentation.[9]

Although we are inclined to doubt that any etiologic role was played by the mercurial diuretics used for therapy, there are some strong traditional arguments in favor of a mercurial etiology: 1. Proteinuria has been known for years to occur in patients repeatedly exposed to small quantities of metallic mercury in the treatment of syphilis.[10] 2. Factory workers exposed to the mercury salt of fulminic acid sometimes develop the clinical picture of nephrosis.[11] 3. Children exposed to calomel-santonin vermifuge[10] and calomel-containing teething powders[12] are reported to have developed nephrosis.

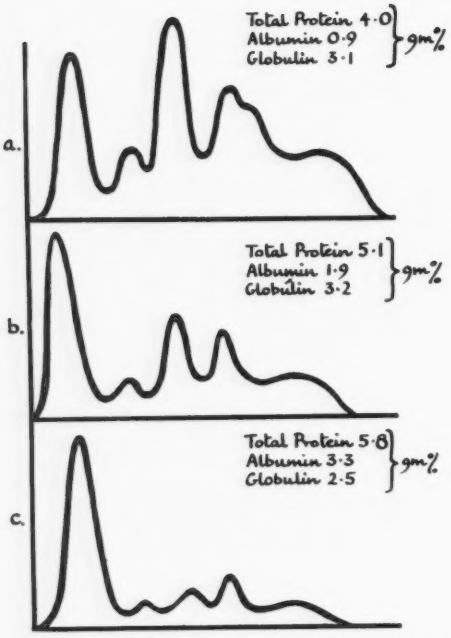

FIG. 6. Electrophoretic patterns of plasma proteins in case 3. *a.* and *b.* Patterns during height of the nephrotic syndrome. *c.* Pattern about 9 months later when nephrotic syndrome had subsided.

On the other hand, we are not aware of any unequivocal evidence that mercurial diuretics employed in the usual therapeutic dosage are able to produce the nephrotic syndrome. Indeed, a controlled study by Coblentz and co-workers[13] demonstrates that parenteral administration of mercurial diuretics in heart failure causes neither a rise in blood nonprotein nitrogen nor an increase in proteinuria, even when azotemia and significant proteinuria are present at the outset of treatment.

Still, it is pertinent to ask whether *orally* administered mercurials are peculiarly likely to cause proteinuria, because it is established that mercury given in this fashion enjoys a significantly delayed excretion and more accumulation within the body than when it is given parenterally.[14, 15] Two of our patients received an oral mercurial at some time before the onset of the nephrotic syndrome, and 1 of Munck and Nissen's cases received an oral mercurial exclusively.

Batterman and co-workers[16] reported that in 4 patients who received oral mercurophylline there was "increasing albuminuria" and "fear of impending generalized mercurialism prompted the cessation of therapy." However, these patients later returned to the hospital in such severe congestive failure that administration of the oral diuretic was re-instituted in spite of the proteinuria. All had a favorable diuretic response and showed "no further evidence of toxicity." This experience is reminiscent of our own.

Kaplan and co-workers[17] found that 5 of 15 patients treated with oral mercurial preparations had proteinuria, but "it could not be attributed to the oral mercurial." No reasons are given to substantiate this opinion, however. Griffith and co-workers[18] followed 12 patients in heart failure for 8 to 65 months while they were treated with the orally administered chlormerodrin, and in no instance did proteinuria occur where it had been absent before the onset of therapy.

We wish to emphasize that in the 3 of our cases that were studied most closely, the nephrotic syndrome disappeared, even though they continued to receive mercurial diuretics. In view of this we do not believe that these patients were at any time suffering kidney damage from mercurial toxicity. Case 4 was not studied as fully as were the first 3 cases, and it is not possible properly to assess the effect of mercurial diuretics in this instance. However, this patient is of interest as another example of the occurrence of nephrotic syndrome without obvious cause in a patient with congestive heart failure.

The Association of Proteinuria and Nephrotic Syndrome with Congestive Heart Failure

It seems preferable to look for the cause of the nephrotic syndrome in the disturbed physiology of heart failure itself. Proteinuria, to be sure, is the rule in congestive failure, and we suggest that in rare instances this proteinuria may be gross enough and prolonged enough to give rise to the nephrotic syndrome.[4, 5] Race and co-workers[19] studied 161 cases of congestive heart failure that came

to autopsy; and of these, 142 were known to have had proteinuria, although in none was there histologic evidence of a significant renal lesion. There was, however, a good correlation between the amount of proteinuria and the clinical severity of congestive heart failure and in 1 case where the proteinuria and degree of failure had been gross, the kidneys were histologically normal. Our own experience is in agreement with these observations.

We can only speculate on how the proteinuria of congestive failure comes about. In general, proteinuria is thought to be associated with increased glomerular filtration of protein,[20, 21] but the part played by tubular dysfunction is uncertain. Current concept holds that minimal glomerular filtration and subsequent tubular reabsorption of protein occur in the normal kidney,[20] and the degree of proteinuria in our cases could be explained by tubular inability to reabsorb the normally filtered protein. However, the absence of serum electrolyte abnormalities or abnormal aminoaciduria (case 3) argue somewhat against tubular abnormality. The situation is complicated by observations that show that globulin as well as albumin is lost by the kidney in congestive heart failure, and the urinary concentration of globulin is alleged to bear no relation to its level in the serum.[22]

Wégria and co-workers[23] have shown in animals that renal congestion causes proteinuria. Proteinuria and nephrotic syndrome occur in man when there is renal vein or inferior vena caval occlusion[6, 24] and has complicated chronic constrictive pericarditis where it has been relieved by pericardiectomy.[24, 25] The detailed chain of events that links venous congestion with proteinuria remains obscure, however. In our cases of nephrotic syndrome there was no impressive correlation between the height of the venous pressure and the degree of proteinuria. Nor have we found the duration of a raised venous pressure to be closely related, for we have seen many patients with prolonged and severe congestive heart failure and tricuspid incompetence who have not developed a nephrotic syndrome.

Whatever the cause of the nephrotic syndrome in these patients, the evidence suggests that mercurial diuretics are not implicated and that the syndrome may be the result of the heart failure itself. In such cases, provided there is no clear evidence of mercurial toxicity, such as a rash, abdominal pain, gingivitis, or evidence of acute renal damage with a suddenly rising blood urea, and provided that a satisfactory diuresis can be produced, mercurial diuretics should not be withheld. Indeed, we suggest that they are definitely indicated. Massive edema and proteinuria in the presence of a normal blood urea and a normal urinary sediment do not by themselves contraindicate their use.

Summary

Attention is drawn to 4 instances of the nephrotic syndrome occurring during the course of chronic heart failure. All developed gross proteinuria, massive edema, hypoalbuminemia, strikingly abnormal plasma electrophoretic patterns, and hypercholesterolemia with a normal or only slightly elevated blood urea and with a normal urinary sediment. Recovery from the nephrotic syndrome occurred in 3 patients over a period of 9 months on a regimen of digitalis, low-salt and high-protein diet, and regular, weekly, intramuscular administration of mercurial diuretics. Aminophylline given intravenously just prior to the mercurial was found to enhance the diuretic response.

Reference is made to the little understood but common phenomenon of proteinuria in heart failure. The possible relationship of the proteinuria to the occasional case of nephrotic syndrome is discussed.

It is concluded that the nephrotic syndrome occurring in chronic heart failure is not caused by mercurial diuretics and is not in itself a contraindication to their continued use.

Acknowledgment

We are grateful to Professor E. J. King and Dr. I. D. P. Wootten for advice on the biochemical aspects of this work and to Dr. Bruce Gutteridge for practical help. Mrs. Angela Birbeck kindly provided the diagrams. We are indebted to Professor J. McMichael and Dr. J. P. Shillingford for permission to quote case 4.

SUMMARIO IN INTERLINGUA

Es presentate 4 casos de syndrome nephrotic, occurrente durante le curso de chronic insufficientia cardiac. Omnes monstrava le disveloppamento de grossier proteinuria, edema massive, hypoalbuminemia, frappante anormalitates del configuration electrophoretic del plasma, e hypercholesterolemia, con normal o levemente elevate nivellos de urea del sanguine e normal sedimentation urinari. In tres del patientes, restablimento ab le syndrome nephrotic occurreva in le curso de un periodo de 9 menses de un regime de digitalis, dieta a basse contento de sal e a alte contento de proteina, e regular administrationes septimanal de diureticos mercurial per via intramuscular. Esseva constatate que le administration de aminophyllina per via intravenose justo ante le administration del diuretico mercurial resultava in un melioration del effecto.

Es signalate le pauco comprendite sed commun phenomeno de proteinuria in insufficientia cardiac. Es discutite le relation possibile inter le proteinuria e le sporadic occurrentia de syndrome nephrotic.

Es concludite que le syndrome nephrotic occurrente in chronic insufficientia cardiac non es causate per diureticos mercurial e non representa per se un indication contra le continuation de lor uso.

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Medical Eponyms

By Robert W. Buck, M.D.

Hanot's Cirrhosis. Victor Charles Hanot (1844-1896) presented "A Study of a Type of Hypertrophic Cirrhosis of the Liver (Hypertrophic Cirrhosis with Chronic Jaundice" (*Étude sur une forme de Cirrhose hypertrophique du foie (Cirrhose hypertrophique avec icters chronique*) to the Paris Faculty of Medicine as his thesis for the doctorate. This is Thesis No. 465 of the Faculty of Medicine of Paris, and was published in 1875. The following quotation is taken from page 89.

"Among the various lesions of the liver which have been included under the name of hypertrophic cirrhosis, there is one which is distinguished by the following features: intralobar sclerosis, abnormal development and chronic catarrh of the smaller bile ducts.

"The clinical form is no less characteristic: It is an affection which first shows itself by chronic jaundice, due to obliteration of the smaller bile ducts, and by a considerable hypertrophy of the liver without ascites or abnormal enlargement of the subcutaneous abdominal veins such as is seen in classic cirrhosis.

"Usually this disease follows a prolonged course, and may continue for several years without any marked alteration in the state of nutrition. It also usually terminates in the syndrome known as icterus gravis.

"By reason of all these peculiarities, it would seem to deserve a separate place in the nosological category. One might term it hypertrophic sclerosis of the liver with chronic jaundice."

An Electrocardiographic Analysis of Sixty-Five Cases of Mitral Regurgitation

By L. G. Bentivoglio, M.D., J. F. Uricchio, M.D., A. Waldow, M.D., W. Likoff, M.D., and H. Goldberg, M.D.

The detailed electrocardiographic analysis of a large series of patients with proved, dynamic mitral regurgitation is lacking in the medical literature. The present report intends to fill the gap and to point out and discuss some discrepancies observed between the current concepts and the results of the study.

ELECTROCARDIOGRAPHY has been long an important tool in cardiac diagnosis and reports of abnormal patterns in patients with rheumatic mitral regurgitation have already appeared in the world literature. The series are, however, either too small[1-5] or lack sufficient surgical or pathologic confirmation[6, 7] of major leak of the mitral valve.

The object of the present report is to present a detailed analysis of the electrocardiographic findings in 65 patients with rheumatic mitral regurgitation of dynamic significance.

Material and Methods

Sixty-five patients with proved dynamic mitral regurgitation constitute the object of the present study. The diagnosis was entertained clinically on the basis of fatigue and dyspnea, a grade III or more blowing systolic murmur at the apex, radiating to the axilla, and a normal to absent mitral first sound. A mid-late rumble at the apex was frequently present. The majority of the patients had also a huge left atrium with a wide sweep of the esophagus on the roentgenograms.

The clinical impression was fortified by the heart catheterization findings in 40 patients. Of these, 23 had right heart catheterization, 11 had left heart catheterization, and 6 had combined heart catheterization. Criteria for suggestion of mitral insufficiency at heart catheterization were the presence of a prominent "c-v" wave either in the pulmonary venous capillary pulse or left atrium, the "wash-out" of the catheter from the left ventricle during systole of this chamber, and a small or absent left atrial-left ventricular filling pressure gradient. When present, the gradient was larger in early diastole and smaller or absent at the end of the ventricular filling period, as previously observed in patients with mitral regurgitation.[8]

Surgery for correction of mitral regurgitation was performed in 64 patients, 2 of whom came later to autopsy. In 1 case postmortem confirmation alone was obtained. In all the operated cases the amount of mitral regurgitation was estimated by the surgeon* to be greater than 2 plus on the basis of 1 to 4 plus. The mitral valve area, estimated at the time of surgery or autopsy, was at least 1½ fingers (2.5 cm.²) in size but less than 2 fingers (4.0 cm.²) in 17 patients, and 2 fingers or more with a maximum of 3½ fingers in all the rest. An area of 2.5 cm.² is well beyond the critical size for dynamic mitral stenosis.

Of the total 65 patients, 22 were male and 43 were female, a ratio of 1 to 2. The ages ranged between 13 and 54 years, with an average of 33 years. The average age for males was 35 years, (22 to 54); for females it was 32, (13 to 51). The distribution of patients according to sex and age groups is reported in table 1.

All the tracings of the present study were recorded on Sanborn electrocardiographs during the period of hospitalization immediately preceding surgery or death (1 case died before surgery) with the patients in the basal state, breathing quietly in the recumbent position.

A 12-lead electrocardiogram was obtained in all cases. The electric axis of the P, QRS, and T waves was measured according to the method of Carter and co-workers.[9] The value of the electric axis of the T wave was approximated to the nearest multiple or submultiple of 15°. The normal axis for the P wave was considered to lie between +45° and +69° of the Carter quadrant; for the QRS interval between +30° and +90°.[10] The electric position was obtained by the criteria of Wilson and co-workers.[11] The duration of waves and intervals is reported in seconds. The magnitude of

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TABLE 1.—*Relative Incidence of Normal Sinus Rhythm and Atrial Fibrillation**

Ventricular patterns	NVC		LVH		RVH		L&RVH		Total	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
NSR	—	8	1	5	—	—	—	1	2	14
AF	7	18	8	5	2	4	—	1	20	29
Total no. pts.	7	26	9	10	2	4	—	2	22	43
Percentage of total	51%		31%		15%		3%		100%	

Age of patients	11–20		21–30		31–40		41–50		51–60	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
NSR	—	4	1	7	—	2	1	1	—	—
AF	—	2	7	8	8	11	4	7	1	1

* Key to abbreviations: NVC, normal ventricular complex; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; L&RVH, left and right ventricular hypertrophy; NSR, normal sinus rhythm; AF, atrial fibrillation.

deflections is given in tenths of millivolts with the instrument adjusted to the usual sensitivity of 1 cm./mV. Durations, magnitude of deflections, and ventricular activation times were calculated according to the recommendations of the committee on electrocardiography of the American Heart Association.[12] Normal standards for the electrocardiogram were considered those given by Kossman.[13] Upper limits of normal for the duration of the Q-T interval in males and females were considered those given by Ashman and Hull.[14] Criteria for left atrial enlargement were considered (1) mean manifest electric axis of atrial activation (ÂP) of less than +45°, (2) duration of the P wave in the peripheral leads of 0.12 second or more, (3) notching of the P wave in the peripheral bipolar leads, and (4) diphasic P wave in which the initial deflection is upward in lead V_1. The criteria of Sokolow and Lyon[15, 16] were used for the diagnosis of left and right ventricular hypertrophy. An S wave in lead V_1 equaling or exceeding 24 mm. was also considered among the criteria for the diagnosis of left ventricular hypertrophy.[17] The criteria of Wilson and co-workers,[11] summarized by Lipman and Massie,[18] were used for the diagnosis of complete left bundle-branch block. The criteria of Barker and Valencia[19] were used for the diagnosis of incomplete right bundle-branch block and incomplete right bundle-branch block

TABLE 2.—*Characteristics of the P Wave and P-R Interval*

Name	P Wave					P-R interval (sec.)	Ventricular complex
	Axis (deg.)	Duration (sec.)	Voltage Lead II	Shape			
				Lead I-II-III	Lead V^1		
J.A.	30	0.12	1.0	Nt.	D	0.21	NVC
K.B.	20	0.14	0.7	Nt.	I	0.18	NVC
M.H.	21	0.14	1.2	R	D	0.20	NVC
E.H.	18	0.12	1.0	Nt.	Nt.	0.18	NVC
B.M.	30	0.10	1.7	R	D	0.17	NVC
E.R.	47	0.11	1.1	R	D	0.19	NVC
M.S.	53	0.12	1.5	R	D	0.18	NVC
M.W.	67	0.11	2.5	P	D	0.18	NVC
M.B.	30	0.13	0.0	Nt.	I	0.19	LVH
E.D.	61	0.16	1.0	R	D	0.21	LVH
J.D.	16	0.13	0.4	Nt.	D	0.22	LVH
H.M.	35	0.13	0.3	Nt.	D	0.16	LVH
L.S.	30	0.13	1.0	Nt.	D	0.14	LVH
M.J.W.	17	0.12	1.0	Nt.	I	0.24	LVH
T.T.	50	0.14	1.5	Nt.	D	0.23	CLBBB
M.P.	46	0.15	2.5	Nt.	R	0.18	L&RVH
Average	32	0.128	1.15	—	—	0.191	—

* Key to abbreviations: NVC, normal ventricular complex; LVH, left ventricular hypertrophy; CLBBB, complete left bundle-branch block; L&RVH, left and right ventricular hypertrophy; Nt., notched; R, rounded; D, diphasic; I, inverted; P, peaked.

associated with right ventricular hypertrophy. The pattern of incomplete left bundle-branch block has not been considered because of the well-known difficulty of differentiating it from left ventricular hypertrophy. No other electrocardiographic patterns were encountered in our series. All but 4 patients (M.H., E.H., E.R., M.W.) were receiving digitalis at the time the electrocardiograms were recorded. The electrocardiograms were analyzed in a tabular form on master sheets and all durations and deflections were carefully measured with the help of calipers and lenses, when necessary. The analysis of the duration and size of the deflections was limited to those leads that are considered representative for the diagnosis of the various electrocardiographic syndromes mentioned above.

RESULTS

Rate and Rhythm. The ventricular rate varied between 52 and 135 beats per minute, with an average of 80. There was no significant difference in the heart rate between patients with normal sinus rhythm and those with atrial fibrillation.

TABLE 3.—*Duration of the QRS Interval**

	NVC		LVH		RVH		IRBBB		CLBBB		L&RVH		RVH & IRBBB		RVH-LVH IRBBB		Total	
	N	PRO	N	PRO	N	PRO	N	PRO	N	PRO	N	PRO	N	PRO	N	PRO	N	PRO
No. pts.	33	—	19	—	6	—	2	1	—	1	1	—	—	1	—	1	61	
Range	0.06	—	0.06	—	0.07	—	0.08	0.11	—	0.16	0.08	—	—	0.11	—	0.11	0.06	0.1
	0.10		0.10		0.09		0.09										0.10	0.16
Mean	0.08	—	0.08	—	0.08	—	0.085	0.11	—	0.16	0.08	—	—	0.11	—	0.11	0.08	0.12
Group	0.06		0.06		0.07		0.08		0.16		0.08		0.11		0.11		0.06	
Range	0.10		0.10		0.09		0.11										0.16	
Mean	0.076		0.08		0.08		0.095		0.16		0.08		0.11		0.11		0.081	

* Key to abbreviations: NVC, normal ventricular complex; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; IRBBB, incomplete right bundle-branch block; CLBBB, complete left bundle-branch block; L&RVH, left and right ventricular hypertrophy; N, normal; PRO, prolonged.

TABLE 4.—*Size of the R wave in the Unipolar Peripheral Leads**

Lead aV_R	NVC		LVH		RVH		IRBBB		CLBBB		L&RHV		RVH& IRBBB		LVH-RVH IRBBB		Total	
	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC
No. pts.	11	—	3	—	4	1	2	1	—	—	1	—	1	—	1	—	23	2
Range	0.2	—	0.3	—	1.0	5.5	1.5	5.0	—	—	1.0	—	3.5	—	2.0	—	0.2	5.0
	2.2		0.5		3.7		3.0										3.7	5.5
Mean	0.7	—	0.4	—	3.4	5.5	2.3	5.0	—	—	1.0	—	3.5	—	2.0	—	1.3	5.3
Group	0.2		0.3		1.0		1.5		—		1.0		3.5		2.0		0.2	
Range	2.2		0.5		5.5		5.0										5.5	
Mean	0.7		0.4		3.0		3.2		—		1.0		3.5		2.0		1.6	
Lead aV_L																		
No. pts.	22	—	18	—	6	—	3	—	1	—	—	—	1	—	1	—	52	—
Range	0.2	—	0.7	—	0.3	—	0.8	—	10.5	--	—	—	1.0	—	3.5	—	0.1	—
	5.0		6.0		1.5		1.3										10.5	—
Mean	2.1	—	2.6	—	0.9	—	1.0	—	10.5	—	—	—	1.0	—	3.5	—	2.1	—
Group	0.2		0.7		0.3		0.8		10.5		—		1.0		3.5		0.1	
Range	5.0		6.0		1.5		1.3										10.5	
Mean	2.1		2.6		0.9		1.0		10.5		—		1.0		3.5		2.1	
Lead aV_F																		
No. pts.	33	—	18	1	6	—	3	—	1	—	1	—	1	—	—	1	63	2
Range	1.5	—	1.0	22.0	5.5	—	5.5	—	2.0	—	19.0	—	6.0	—	—	20.5	1.0	20.5
	15.5		17.0		13.5		14.0										19.0	22.0
Mean	8.2	—	8.9	22.0	9.4	—	9.7	—	2.0	—	19.0	—	6.0	—	—	20.5	8.6	21.3
Group	1.5		1.0		5.5		5.5		2.0		19.0		6.0		20.5		1.0	
Range	15.5		22.0		13.5		14.0										22.0	
Mean	8.2		9.6		9.4		9.7		2.0		19.0		6.0		20.5		9.0	

* Key to abbreviations: NVC, normal ventricular complex; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; IRBBB, incomplete right bundle-branch block; CLBBB, complete left bundle-branch block; L&RVH, left and right ventricular hypertrophy; N, normal; INC, increased.

Sixteen patients (25 per cent) showed normal sinus rhythm. Two of these (12 per cent) were males and 14 (88 per cent) females. The incidence of normal sinus rhythm was 9 per cent among males and 32 per cent among females (table 1).

Atrial and Ventricular Complexes. The data concerning the P waves, P-R intervals, and QRS complexes are presented in tables 2-9. Thirty-three patients showed a normal ventricular complex, 19 showed a pattern of left ventricular hypertrophy, 6 showed right ven-

TABLE 5.—*Size of the R Wave in the Representative Unipolar Precordial Leads**

Lead	NVC		LVH		RVH		IRBBB		CLBBB		L&RVH		RVH& IRBBB		LVH-RVH IRBBB		Total	
	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC
No. pts.	20	—	14	—	5	1	2	1	—	—	—	1	—	—	—	1	41	5
Range	0.2	—	0.5	—	0.5	7.0	1.0	7.5	—	—	—	27.0	—	10.5	—	11.0	0.2	7.0
	4.5		4.5		2.5		2.0										4.5	27.0
Mean	1.1	—	1.5	—	1.7	7.0	1.5	7.5	—	—	—	27.0	—	10.5	—	11.0	1.1	12.6
Group	0.2		0.5		0.5		1.0		—		27.0		10.5		11.0		0.2	
Range	4.5		4.5		7.0		7.5		—								27.0	
Mean	1.1		1.5		2.6		3.5		—		27.0		10.5		11.0		26.0	
Lead V5																		
No. pts.	33	—	10	9	6	—	3	—	1	—	—	1	1	—	—	1	54	11
Range	4.0	—	14.5	26.0	1.0	—	5.0	—	16.0	—	—	27.5	11.0	—	—	38.0	1.0	26.0
	19.0		25.5	46 0	23.0		9.0										25.5	46.0
Mean	12 3	—	21.0	32.1	11.7	—	7.3	—	16.0	—	—	27.5	11.0	—	—	38.0	13.6	32.2
Group	4.0		14.5		1.0		5.0		16.0		27.5		11.0		38.0		1.0	
Range	19.0		46.0		23.0		9.0										46.0	
Mean	12.3		26.3		11.7		7.3		16.0		27.5		11.0		38.0		16.8	
Lead V6																		
No. pts.	33	—	14	5	6	—	3	—	1	—	1	—	1	—	—	1	59	6
Range	4.5	—	12 0	26.0	1.0	—	5.5	—	15.0	—	21.5	—	7.5	—	—	34.0	1.0	26.0
	22.5		2.45	36.0	16.0		14.5										24.5	36.0
Mean	11.4	—	17.4	29.0	8.4	—	9.0	—	15.0	—	21.5	—	7.5	—	—	34.0	12.6	29.8
Group	4.5		12.0		1.0		5.5		15.0		21.5		7.5		34.0		1.0	
Range	22.5		56.0		16.0		14.5										36.0	
Mean	11.4		20.5		8.4		9.0		15.0		21.5		7.5		34.0		14.2	

* Key to abbreviations: NVC, normal ventricular complex; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; IRBBB, incomplete right bundle-branch block; CLBBB, complete left bundle-branch block; L&RVH, left and right ventricular hypertrophy; N, normal; INC, increased.

tricular hypertrophy, 3 showed incomplete right bundle-branch block, and 1 each showed left bundle-branch block, combined right and left ventricular hypertrophy, right ventricular hypertrophy and incomplete right bundle-branch block, right and left ventricular hypertrophy and incomplete right bundle-branch block (tables 2-9).

DISCUSSION

The sixty-five cases reported represent patients with proved, functionally pure, and advanced mitral regurgitation. The results of the present analysis are in partial disagreement with previous reports[6, 7] and current teaching.[20] Preceding series[6, 7] admittedly included cases diagnosed only on clinical grounds. The difficulty in distinguishing major mitral regurgitation from combined mitral stenosis and regurgitation by clinical methods alone is generally appreciated. Tricuspid regurgitation can also masquerade as mitral regurgitation in patients with pure mitral stenosis.[21] It is for these reasons that special diagnostic studies including cardiac ventriculography and left heart catheterization often must be employed to establish more exactly the amount of obstruction and leak. Electrocardiographic reports on patients with rheumatic mitral valve disease in which these tests are not performed, or in which direct palpation of the valve at surgery is not carried out, can justifiably be viewed with skepticism. Another factor to be considered is the generally advanced stage of the disease in our group as judged by the higher incidence of atrial fibrillation. These considerations supply possible explanations for some discrepancies encountered between this and previous reports.

A rheumatic etiology was established in our cases, based on positive historical data, biopsy of atrial appendages, and autopsy findings.

TABLE 6.—*Duration of the Ventricular Activation Time**

Lead V_1–V_2	NVC		LVH		RVH		IRBBB		CLBBB		L&RVH		RVH & IRBBB		RVH–LVH IRBBB		Total	
	N	PRO	N	PRO	N	PRO	N	PRO	N	PRO	N	PRO	N	PRO	N	PRO	N	PRO
No. pts.	28	—	19	—	1	5	—	3	—	—	1	—	—	1	—	1	49	1
Range	0.01	—	0.01	—	0.01	0.04	—	0.05	—	—	0.02	—	—	0.08	—	0.09	0.01	0.04
	0.03		0.03			0.06		0.08									0.03	0.09
Mean	0.02	—	0.02	—	0.01	0.05	—	0.06	—	—	0.02	—	—	0.08	—	0.09	0.02	0.06
Group	0.01		0.01		0.01		0.05		—		0.02		0.08		0.09		0.01	
Range	0.03		0.03		0.06		0.08										0.09	
Mean	0.02		0.02		0.04		0.06		—		0.02		0.08		0.09		0.03	
Lead V_3–V_6																		
No. pts.	33	—	5	14	6	—	3	—	—	1	1	—	1	—	—	1	48	17
Range	0.03	—	0.04	0.06	0.02	—	0.03	—	—	0.07	0.05	—	0.05	—	—	0.06	0.02	0.05
	0.05		0.05	0.07	0.04		0.04										0.05	0.07
Mean	0.04	—	0.05	0.06	0.03	—	0.03	—	—	0.07	0.05	—	0.05	—	—	0.06	0.04	0.06
Group	0.03		0.04		0.02		0.03		0.07		0.05		0.05		0.06		0.02	
Range	0.05		0.07		0.04		0.04										0.07	
Mean	0.04		0.06		0.03		0.03		0.07		0.05		0.05		0.06		0.05	

* Key to abbreviations: NVC, normal ventricular complex; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; IRBBB, incomplete right bundle-branch block; CLBBB, complete left bundle-branch block; L&RVH, left and right ventricular hypertrophy; N, normal; PRO, prolonged.

TABLE 7.—*Size of the S Wave in the Representative Precordial Leads**

S Wave Lead V_1	NVC		LVH		RVH		IRBBB		CLBBB		L&RVH		RVH & IRBBB		LVH–RVH IRBBB		Total	
	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC
No. pts.	22	—	17	—	1	—	2	—	—	—	—	1	—	—	1	—	43	1
Range	3.0	—	3.0	—	2.0	—	5.0	—	—	—	—	34.0	—	—	6.0	—	2.0	34.0
	11.0		16.0				6.3										19.0	
Mean	7.5	—	9.9	—	2.0	—	5.7	—	—	—	—	34.0	—	—	6.0	—	8.2	34.0
Group	3.0		3.0		2.0		5.0		—		34.0		—		6.0		2.0	
Range	11.0		16.0				6.3										34.0	
Mean	7.5		9.9		2.0		5.7		—		34.0		—		6.0		9.4	
S Wave Lead V_3																		
No. pts.	12	3	5	—	1	5	—	3	1	—	—	—	—	1	1	—	20	12
Range	0.5	7.5	1.0	—	6.5	7.0	—	7.5	1.1	—	—	—	—	13.5	1.5	—	0.5	7.0
	6.5	15.0	2.5			11.5		14.0									6.5	15.0
Mean	4.6	12.0	1.4	—	6.5	10.3	—	11.5	1.1	—	—	—	—	13.5	1.5	—	3.4	11.7
Group	0.5		1.0		6.5		7.5		1.1		—		13.5		1.5		0.5	
Range	15.0		2.5		11.5		14.0										15.0	
Mean	4.6		1.4		9.7		11.5		1.1		—		13.5		1.5		5.8	
S Wave Lead V_6																		
No. pts.	4	—	—	—	5	1	1	2	—	—	—	—	1	—	1	—	12	3
Range	0.5	—	—	—	0.5	7.5	2.2	8.0	—	—	—	—	5.5	—	1.0	—	0.5	7.5
	6.0				6.5			15.5									6.5	15.5
Mean	3.3	—	—	—	3.4	7.5	2.2	11.8	—	—	—	—	5.5	—	1.0	—	3.5	10.3
Group	0.5		—		0.5		2.2		—		—		5.5		1.0		0.5	
Range	6.0				7.5		15.5										15.5	
Mean	3.3		—		4.1		8.6		—		—		5.5		1.0		4.9	

* Key to abbreviations: NVC, normal ventricular complex; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; IRBBB, incomplete right bundle-branch block; CLBBB, complete left bundle-branch block; L&RVH, left and right ventricular hypertrophy; N, normal; INC, increased.

Females were encountered twice as commonly as males. The mean age for the 2 sexes was approximately the same and fell within the first half of the fourth decade of life.

In contrast with previous reports[6, 7] atrial fibrillation was encountered in 3 out of 4 patients. This is a higher incidence than the 1:3 ratio reported for patients with proved mitral stenosis and it is probably related to the marked dilatation of the left atrium usually present in mitral regurgitation. The frequency of atrial fibrillation was directly proportional in a linear fashion to the age of the patients and, presumably, to the duration of the disease. It occurred in 90 per cent of the males and 66 per cent of the females.

Normal sinus rhythm was found exclusively and in equal proportion among patients with a normal ventricular complex or left ventricular hypertrophy (and in 1 patient with combined ventricular hypertrophy). The atrial complex of all the patients fulfilled at least one of the criteria for the diagnosis of left atrial enlargement. This is in contrast with the normal P waves reported in previous studies.[6, 7]

For a consideration of the ventricular complex the patients were classified into 4 groups: normal ventricular complex, left ventricular hypertrophy, combined ventricular hypertrophy, and right ventricular hypertrophy. This grouping was made not only for greater simplicity but also with the realization that some electrocardiographic patterns, although morphologically different, merely represent progressive stages of an identical process. It has been repeatedly emphasized, for instance, that incomplete or complete bundle-branch block, obtained in a ventricle performing an increased amount of work, may be considered as the expression of ventricular hypertrophy.[22, 23] Rheumatic mitral regurgitation, in its typical form, initially increases the work of the left ventricle. Subsequently, with the production of vascular changes in the pulmonary circuit, the right ventricle is subjected to an increased load. It seems quite logical, therefore, to group left ventricular hypertrophy and left bundle-branch block together and to do the same for the right ventricular

TABLE 8.—*R/S Ratios in Precordial Leads**

R/S Ratio in Lead V_1	NVC			LVH			RVH			IRBBB			CLBBB			L&RVH			RVH IRBBB			RVH-LVH IRBBB			Total		
	N	INC	DEC	N	INC	DEC	N	INC	DEC	N	INC	DEC	N	INC	DEC	N	INC	DEC	N	INC	DEC	N	INC	DEC	N	INC	DEC
No. pts.	20	—	—	4	—	—	1	—	—	1	1	—	—	—	—	1	—	—	—	—	—	1	—	—	37	2	—
Range	0.03	—	—	0.05	—	—	0.25	—	—	0.20	1.20	—	—	—	—	0.80	—	—	—	—	—	1.83	—	—	0.02	1.20	—
	0.56			0.32																					0.56	1.83	
Mean	0.15	—	—	0.15	—	—	0.25	—	—	0.20	1.20	—	—	—	—	0.80	—	—	—	—	—	1.83	—	—	0.15	1.51	—
Group		0.03			0.05			0.25			0.20			—			0.80			—			1.83			0.02	
Range		0.56			0.32																					1.83	
Mean		0.15			0.15			0.25			0.20			—			0.80			—			1.83			0.22	
R/S Ratio in Lead V_5-V_6																											
No. pts.	15	—	—	3	2	—	5	—	1	2	—	1	1	—	—	—	—	—	1	—	—	—	1	—	27	3	2
Range	1.50	—	—	9.50	26.0	—	1.46	—	0.73	1.06	—	0.35	14.5	—	—	—	—	—	1.36	—	—	—	34.0	—	1.06	26.0	0.35
	16.2			20.0	42.0		6.40			1.80															20.0	42.0	0.73
Mean	6.26	—	—	15.4	34.0	—	2.82	—	0.73	1.43	—	0.35	14.5	—	—	—	—	—	1.36	—	—	—	34.0	—	6.40	34.0	0.54
Group		1.50			9.50			0.73			0.35			14.5			—			1.36			34.0			0.35	
Range		16.2			42.0			6.40			1.80															42.0	
Mean		6.26			22.8			2.47			1.07			14.5			—			1.36			34.0			8.62	
R/S in V_5 over R/S in V_1 Ratio																											
No. pts.	6	—	—	—	5	—	1	—	—	2	—	—	—	—	—	—	—	—	—	—	—	1	—	—	10	5	—
Range	5.80	—	—	—	110	—	0.35	—	—	0.88	—	—	—	—	—	—	—	—	—	—	—	18.5	—	—	0.35	110	—
	100				260					9.00															100	260	
Mean	40.3	—	—	—	193	—	0.35	—	—	4.94	—	—	—	—	—	—	—	—	—	—	—	18.5	—	—	27.0	193	—
Group		5.80			110			0.35			0.88			—			—			—			18.5			0.35	
Range		100			260						9.00															260	
Mean		40.3			193			0.35			4.94			—			—			—			18.5			82.5	

*Key to abbreviations: NVC, normal ventricular complex; LVH, left ventricular hypertrophy; RVH, right bundle-branch block; CLBBB, complete left bundle-branch block; L&RVH, left and right ventricular hypertrophy; N, normal; INC, increased; DEC, decreased.

TABLE 9.—*Sums of R and S Waves in Precordial Leads**

	NVC		LVH		RVH		IRBBB		CLBBB		L&RVH		RVH IRBBB		LVH-RVH IRBBB		Total	
	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC	N	INC
R Wave in V_1+S Wave in V_5-V_6																		
No. pts.	7	—	5	—	5	1	2	1	—	—	—	—	—	1	—	1	18	4
Range	1.0	—	1.5	—	0.9	14.5	9.0	17.5	—	—	—	—	—	16.0	—	12.0	0.9	1.0
	6.5		4.0		9.0		9.7										9.7	1.5
Mean	3.5	—	2.8	—	5.9	14.5	9.4	17.5	—	—	—	—	—	16.0	—	12.0	4.7	1.0
Group	1.0		1.5		0.9		9.0		—		—		16.0		12.0		0.9	
Range	6.5		4.0		14.5		17.5										17.5	
Mean	3.5		2.8		7.4		12.1		—		—		16.0		12.0		6.9	
R Wave in V_5-V_6+S Wave in V_1																		
No. pts.	33	—	8	11	1	—	2	—	—	1	—	1	—	—	—	1	44	1
Range	10.0	—	18.0	35.5	3.0	—	14.3	—	—	52.0	—	61.5	—	—	—	40.0	3.0	35.5
	31.5		33.0	60.0			19.5										33.0	60.5
Mean	20.7	—	26.9	42.6	3.0	—	16.9	—	—	52.0	—	61.5	—	—	—	40.0	21.2	48.5
Group	10.0		18.0		3.0		14.3		52.0		61.5		—		40.0		3.0	
Range	31.5		60.0				19.5										61.5	
Mean	20.7		36.0		3.0		16.9		52.0		61.5		—		40.0		26.8	

* Key to abbreviations: NVC, normal ventricular complex; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; IRBBB, incomplete right bundle-branch block; CLBBB, complete left bundle-branch block; L&RVH, left and right ventricular hypertrophy; N, normal; INC, increased.

hypertrophy and incomplete right bundle-branch block.

In disagreement with the current concepts and teachings, which stress the frequent occurrence and diagnostic value of left axis deviation in mitral insufficiency,[7, 20] the present study revealed the mean manifest electric axis of ventricular activation (ÂQRS) to be either normal or deviated to the right and the electric position to be intermediate to vertical in the great majority of cases. Left axis deviation and semihorizontal or horizontal position were found almost exclusively among patients with left ventricular hypertrophy and in a few cases with normal ventricular complex. No patients with left ventricular hypertrophy showed right axis deviation and conversely no patients with right ventricular hypertrophy showed left axis deviation.

A normal ventricular complex was present in 50 per cent of the total series. The female to male ratio was 4:1 in this group. Soulié and co-workers[6] found at right heart catheterization increased pulmonary resistance in a few cases with normal ventricular complexes and suggested that they may represent patterns of balanced left and right ventricular hypertrophy. A normal ventricular complex could therefore be the resultant of well-balanced potentials in hypertrophy of both ventricles. These considerations probably apply also to the present series and some of the normal tracings may belong in the group of combined left and right ventricular hypertrophy, which is unexpectedly small. Theoretically one would expect a higher incidence of combined rather than right ventricular hypertrophy in mitral regurgitation. From a quantitative point of view the electrocardiogram of mitral regurgitation may be represented by a pyramid where the base is made up by the normal ventricular complex and the apex by the right ventricular hypertrophy pattern with left and combined ventricular hypertrophy in between.

Left ventricular hypertrophy was present in approximately 30 per cent of our series. This lower incidence in comparison to previous reports[6, 7] is explicable probably by our close adherence to the rigid criteria of Sokolow and Lyon[15, 16] and Wilson and associates,[11] which have been shown to be highly accurate in a recent anatomic-electrocardiographic correlative study.[24] In some instances[6] the sole evidence of left ventricular hypertrophy consists of RS-T and T changes.

These changes, however, could be ascribable to digitalis effect rather than ventricular hypertrophy. In none of our cases was the diagnosis of left ventricular hypertrophy based on these changes alone. In this way false positives are eliminated, although a few patients with varying degrees of left ventricular enlargement may be excluded from this group.

Combined left and right ventricular hypertrophy was encountered in only 2 patients, or 3 per cent of our total group, against 37 per cent in the series by Soulié. Here again Soulié reported as typical of combined ventricular hypertrophy a tracing that seems to indicate only right ventricular hypertrophy.

The pattern of right ventricular hypertrophy comprised 15 per cent of the present series. The pathophysiologic and clinical features of some of these patients have been analyzed in a previous report.[25] The finding of right ventricular hypertrophy in mitral insufficiency in a relatively high number of cases is certainly unusual and in sharp contrast with the present teaching. It is important to emphasize that right ventricular hypertrophy is not an unusual feature of rheumatic mitral regurgitation. Its presence, therefore, in patients with mitral valve disease is of less value than other clinical features in the differentiation between mitral stenosis and regurgitation.

Summary

The electrocardiographic data of 65 proved cases of dynamically significant mitral regurgitation are presented. In the present series rheumatic fever was the common etiologic factor. Females were encountered twice as often as males. Atrial fibrillation was observed in 3 out of 4 patients and evidence of left atrial enlargement was constant when sinus rhythm was present. The axis of the QRS complex was normal or deviated to the right in most instances. The ventricular complex was normal in 50 per cent of the cases while left ventricular hypertrophy occurred in 30 per cent, right ventricular hypertrophy in 15 per cent, and combined ventricular hypertrophy in 5 per cent of the cases.

Discrepancies between the present and previous series are discussed and possible explanations for them and for the lower than expected incidence of combined ventricular hypertrophy are proposed.

Acknowledgment

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Summario in Interlingua

Es presentate le datos electrocardiographic ab 65 provate casos de regurgitation mitral de grados dynamicamente significative. In iste serie, febre rheumatic esseva le factor etiologic commun. Femininas esseva duo vices plus frequente que masculos. Fibrillation atrial esseva observate in 3 ex omne 4 patientes, e signos de allargamento sinistro-atrial esseva presente in omne casos con rhythmo sinusal. In le majoritate del casos, le axe del complexo QRS esseva normal o deviava in direction dextrorse. Le complexo ventricular esseva normal in 50 pro cento del casos. Hypertrophia sinistro-ventricular occurreva in 30 pro cento, hypertrophia dextero-ventricular in 15 pro cento, e hypertrophia ventricular combinate in 5 pro cento del casos.

Discrepantias inter le presente e previe series es discutite. Es proponite explicationes possibile pro illos e etiam pro le inexpectatemente basse incidentia de hypertrophia ventricular combinate.

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The Splanchnic Blood Volume in Congestive Heart Failure

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With the technical assistance of Pasquale Cifarelli and Armen Renjilian

Little data have been accumulated regarding the contribution of regional volumes to the increased total blood volume observed in congestive heart failure. This report deals with the measurement of splanchnic blood volume in 12 patients in congestive heart failure compared with results obtained in 10 control subjects similarly studied.

THE total blood volume in congestive heart failure has been the subject of extensive investigation. Although there are isolated reports failing to demonstrate a consistently increased volume,[1, 2] the overwhelming body of evidence obtained with both plasma[3–5] and red-cell tags[3, 6–8] leaves little doubt that total blood volume is increased in the majority of patients having overt evidence of congestive heart failure.

Lack of suitable methodology has limited the knowledge of the contribution of various regional volumes to total blood volume. An exception is the attention that has been focused on the cardiopulmonary blood volume measured by the Stewart-Hamilton indicator-dilution technic. An expanded cardiopulmonary blood volume in association with heart failure has been found by Kopelman and Lee,[9] by Borden, Ebert, Wilson and Wells,[10] and by Doyle, Wilson, Lepine and Warren.[11]

Bradley, Marks, Reynell and Meltzer[12] have recently introduced a method of measurement of splanchnic blood volume. The purpose of the study here described was to assess the possibility that an expanded splanchnic blood volume contributes to the increased total blood volume in patients manifesting congestive heart failure.

METHODS AND PROCEDURES

Splanchnic plasma volume (T 1824 space) was measured in 12 patients with moderate-to-severe congestive heart failure, and splanchnic blood volume was approximated by use of the hematocrit level of blood from a large vessel. Similar studies were made of 10 normal control subjects of comparable age. The normal cases either had been hospitalized for study of nonorganic complaints or were convalescing from minor illnesses; none had evidence of significant cardiovascular disease. All patients and controls were males. Studies were carried out in the fasting, unsedated state and with the subject recumbent. A priming dose of 100 mg. bromsulphalein was injected intravenously, following which a solution of bromsulphalein in 5 per cent dextrose in water was infused at a constant rate with a Bowman pump. An average of 3.9 mg. of bromsulphalein per minute was administered. Right heart catheterization was performed in the usual manner, after which the catheter was placed in a branch of the right hepatic vein. Pressures were recorded in the wedged and free positions. Three to 4 brachial arterial and hepatic vein samples were then simultaneously withdrawn at 8- to 10-minute intervals for determination of hepatic blood flow. Samples were also taken midway through the last period for oxygen analysis. One minute after withdrawal of the last samples, a measured amount of T 1824 was injected intravenously. Coincident with injection, sampling was begun from the brachial artery and hepatic vein by means of a constant suction pump.[13] Multiple samples were collected continuously at 45-second intervals for a period of 225 to 280 seconds. Samples for determination of total blood volume were obtained at 10 and 20 minutes after injection or occasionally at 20 and 30 minutes. Samples taken for bromsulphalein analyses were centrifuged and a 1:10 dilution of plasma was analyzed in duplicate in a Coleman colorimeter at a wavelength of 580 mμ. following addition of 1 to 2 drops of 10 per cent sodium hydroxide. The samples collected for T 1824 dye analyses were centrifuged, and the undiluted plasma was analyzed in a Beckman D. U. spectophotometer at a wavelength of 620 mμ. Hematocrit levels were corrected for trapped plasma as suggested by Gregersen.[14] Oxygen analyses were performed by the method of Van Slyke and Neill.[15] Cardiac output was determined by the direct Fick

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TABLE 1.—*Hemodynamic Data in Twelve Patients with Congestive Heart Failure*

Patient	Diagnosis	Age (yrs.)	Weight (Kg.)	Surface Area (M^2)	Total O_2 consumption (ml./min./M^2)	Arterial-mixed venous O_2 difference (ml./L.)	Direct Fick cardiac index (L./min./M^2)	Pressures			
								B.A. (mm. Hg)	P.A. (mm. Hg)	R.A. (mm. Hg)	Wedged hepatic vein (mm. Hg)
G.C.	H.C.V.D.	62	55.7	1.55	154	63	2.5	209/104	53/23	5	8
H.F.	Cor P.	62	63.4	1.76	112	40	2.8	135/73	41/22	6	9
A.H.	R.H.D.	61	55.9	1.61	139	43	3.2	157/73	50/21	9	13
G.K.	Cor P.	47	78.0	1.94	149	51	2.9	119/82	28/20	6	8
J.M.	Cor P.	66	63.6	1.75	125	53	2.4	128/77	52/28	7	14
B.M.	R.H.D.	41	79.1	2.00	131	92	1.4	122/83	112/53	18	20
W.P.	R.H.D.	60	72.3	1.92	155	84	1.8	152/95	83/41	15	18
J.P.	Cor P.	61	89.5	2.05	131	69	1.9	119/70	73/40	15	19
E.S.	Cor P.	60	70.9	1.88	82	56	1.5	136/78	67/27	6	8
J.Z.	A.S.H.D.	61	75.5	1.89	134	—	—	———	———	15	15
W.K.	R.H.D.	47	65.0	1.72	125	106	1.2	109/68	68/43	12	15
C.B.	A.S.H.D.	30	70.5	1.82	199	75	2.7	126/76	66/40	20	20

B.A., brachial artery; P.A., pulmonary artery; R.A., right atrium; H.C.V.D., hypertensive cardiovascular disease; Cor P., cor pulmonale; R.H.D., rheumatic heart disease; A.S.H.D., arteriosclerotic heart disease.

method. Estimated hepatic blood flow was calculated by the method of Bradley and associates.[10] Values obtained only during periods when the plasma bromsulphalein concentration was changing at a rate of less than 0.0003 mg. per minute were utilized. Splanchnic blood volume was calculated according to the method introduced by Bradley[12] as modified for errors in delay time or collection as suggested by Rabinowitz and Rapaport.[13] Equilibration was assumed to have occurred when hepatic and arterial concentrations of T 1824 approached to within 5 per cent of equality and did not significantly diverge thereafter. The ratio of hepatic vein-arterial concentration difference in the equilibration samples to the final equilibration concentration averaged 2.1 per cent.

RESULTS

The results of this study are summarized in tables 1 and 2. The coefficient of variability is significantly less when the splanchnic and total blood volumes are calculated at the time of study in terms of body weight rather than body surface area. Therefore the volumes in table 2 are expressed in ml. per Kg. The flow data in tables 1 and 2 are corrected for body surface area, as is customary.

Although therapeutic measures had been started in most of the cases of congestive failure, edema was still present in all at the time of cardiac catheterization. Only 1 patient (C. B.) had apparent ascites; however, all demonstrated palpable hepatomegaly. The pulse rate was under 100 beats per minute in all except 1 (C. B.), in whom the rate was 130 at the time of study.

Cardiac output was significantly reduced in the patients with congestive heart failure. Cardiac index in this group ranged from 1.2 to 3.2 L. per minute per $M.^2$ with a mean of 2.2 (S.D. 0.65). Mean cardiac index in the normal controls was 3.4 L. per minute per $M.^2$ (S.D. 0.59) with a range between 2.5 and 4.4 L. per minute per $M.^2$

Estimated hepatic blood flow averaged 813 ml. per minute per $M.^2$ (S.D. 143) among the normal subjects. Five of the 12 patients with congestive heart failure had values less than 536 ml. per minute per $M.^2$, or below the normal mean, less approximately 2 standard deviations. The relatively large variability in the remaining cases and the small series involved resulted in an inability to demonstrate a statistically significant reduction in the estimated hepatic blood flow among the

congestive heart failure patients as a group. The average flow in the heart failure cases was 674 ml. per minute per M.^{2} (S.D. 257). The differences between the means of the 2 groups is 1.5 times the standard error of the differences of the means.

Splanchnic oxygen consumption was similar in the 2 groups, averaging 41.7 ml. per M.^{2} (S.D. 11) in the normal subjects and 42.6 (S.D. 4.3) in the failure group. Mean arterial-hepatic venous oxygen difference was 71 ml. per L. (S.D. 32) in the congestive heart failure group as contrasted to a mean of 51 ml. per L. (S.D. 10) in the normal group.

Total blood volume was markedly elevated in the congestive heart failure group and averaged 79.8 ml. per Kg. (S.D. 12.5) compared to a mean of 62.1 ml. per Kg. (S.D. 7) in the normal group. Splanchnic blood volume (average 20.8 ml. per Kg., S.D. 5.6) was similarly increased among the patients with congestive heart failure compared to the normal subjects (12.7 ml. per Kg., S.D. 2.2). The differences of both parameters are statistically highly significant.

Comments

Blood Flow

Cardiac output was reduced in this group of patients with congestive heart failure. This finding is in agreement with a number of previous studies.[17-20]

It was of interest that the reduction in estimated hepatic blood flow in 5 of the 12 cases in which it occurred was roughly proportional to the reduction in cardiac output. Thus the ratio of estimated hepatic blood flow to cardiac output either remained normal or was increased in the group with congestive heart failure over the normal controls. Myers and Hickam[17] found an estimated hepatic blood flow significantly reduced in patients with congestive heart failure. They noted that the fall in hepatic blood flow was proportional to the fall in cardiac output. The importance of these observations is that they suggest no mechanism for selective reduction in splanchnic blood flow in patients with congestive failure. They serve to emphasize that maintenance of hepatic blood flow is important to the body economy and that the reduction that may occur in congestive heart failure is not out of proportion to the general reduction in cardiac output. In this respect the action of the splanchnic bed differs strikingly from that of the kidney, where a reduction in blood flow occurs much out of proportion to the reduction in cardiac output in patients with congestive heart failure.[20]

There was close agreement between splanchnic oxygen uptake in the normal control group and that in the patients with congestive heart failure. Since hepatic blood flow tended to be reduced, it follows that the extraction of oxygen by the splanchnic bed was greater in the congestive heart failure group than in the controls.

The extraction ratios of bromsulphalein averaged 36 per cent (range 15 to 60 per cent) in the failure patients compared to 40 per cent (range 18 to 74 per cent) in the controls. In no case did extraction fall below 15 per cent, and therefore the validity of the flow data was not considered jeopardized. Extraction ratios of bromsulphalein vary inversely with the arterial concentration. Thus the absence of an apparent difference between the 2 groups of subjects is misleading. When the data are expressed as milliliters of arterial plasma completely cleared of bromsulphalein per minute per M.^{2} (table 2), a definite impairment in the ability of the congestive heart failure group to remove bromsulphalein is seen. Bromsulphalein clearance averaged 205 ml. of plasma per minute per M.^{2} (S.D. = 89) in the normal group as compared to 116 ml. per minute per M.^{2} (S.D. = 55) in the group with congestive heart failure ($p = .01$).

Blood Volume

The basic tenets of the Bradley method for determination of splanchnic blood volume are described in detail elsewhere.[12] Among these is the assumption that all the plasma tag within the splanchnic bed remains in the intravascular space during the 4 minutes or so necessary for equilibration. This assumption

TABLE 2.—*Hemodynamic Data of Hepatic and Splanchnic Circulation in 12 Patients with Congestive Heart Failure*

Patient	Estimated hepatic blood flow (ml./min./M.²)	Ratio hepatic blood flow/cardiac output (%)	Arterial-/hepatic venous O_2 difference (ml./L.)	Splanchnic O_2 uptake (ml./min./M.²)	Splanchnic blood vol. (ml./Kg.)	Total blood vol. (ml./Kg.)	Ratio splanchnic blood vol./total blood vol. (%)	Derived mean transit time (sec.)	Plasma BSP clearance (ml./min./M.²)	[illegible]
G.C.	748	30.5	62	46.4	15.1	84.1	18.0	43.6	77	48.5
H.F.	838	30.0	50	41.9	13.9	79.0	17.7	36.0	127	56.6
A.H.	1101	34.2	41	45.2	28.6	92.6	30.9	54.1	101	38.7
G.K.	725	24.8	57	41.3	16.4	54.5	30.1	54.6	200	49.9
J.M.	978	41.4	40	39.1	28.7	67.3	42.7	64.0	145	52.5
B.M.	427	30.1	82	35.0	24.8	98.6	25.1	137.6	38	44.4
W.P.	323	17.5	113	36.5	26.6	96.2	27.6	185.9	78	46.9
J.P.	941	49.6	44	41.4	18.7	70.3	26.6	52.0	225	43.2
E.S.	752	51.0	67	50.4	13.1	78.5	16.6	39.3	106	49.3
J.Z.	347	——	138	47.8	17.0	90.0	18.9	117.9	109	42.7
W.K.	375	31.8	113	42.4	23.0	71.0	32.3	138.8	43	47.3
C.B.	535	20.1	44	43.3	23.8	75.4	31.4	103.6	147	45.6
Congestive failures										
Mean	674	32.8	71	42.6	20.8	79.8	26.5	85.6	116	
S. D.	257	10.3	32	4.3	5.6	12.5	7.4	47.3	55	
Normal										
Mean	813	25.7	51	41.7	12.7	62.1	20.8	36.9	205	
S. D.	143	7.7	10	11.0	2.2	7.0	5.1	7.5	89	
Significance of differences in means	$p>.1$	$.1>p>.05$	$p=.05$	$p>.1$	$p<.01$	$p<.01$	$.05>p>.01$	$p<.01$	$p=.01$	

may be a tenuous one in respect to patients with congestive heart failure, where some extravascular loss and removal by lymphatic drainage could occur during this interval. However, Milnor and Crary[21] were unable to demonstrate evidence of rapid loss of T 1824 from the plasma of patients with congestive heart failure; unfortunately their methods were not designed to study the disappearance rate during the first 2 to 4 minutes after injection. Samet and co-workers[22] concluded that an abnormal rate of plasma T 1824 loss is unlikely in patients with congestive heart failure, since the concentration obtained by extrapolating to zero time was independent of the amount of dye injected or of the time interval over which the injection was made. Calculations in our cases based on subsequent disappearance slopes of dye concentrations, and the assumption that approximately 25 per cent of the total loss took place in the splanchnic bed, together with the observation that hepatic venous concentration of T 1824 is not demonstrably lower than the arterial following equilibration, suggest that splanchnic extravascular loss during the first 4 minutes is not sufficient to affect materially the calculated volumes. The defense of plasma tags for measurement of total blood volume by Schreiber and co-workers[3] in patients with

congestive heart failure is particularly applicable, because the total duration of measurement from injection to regional equilibration is brief.

The use of any plasma tag and the large vessel hematocrit for calculation of splanchnic blood volume will result in values somewhat greater than those that actually exist, because the ratio of splanchnic to large vessel hematocrit is less than unity. Comparisons by Lilienfield and associates,[23] of mean circulation times across the splanchnic bed following simultaneous injection of plasma and red cell tags suggest that this ratio is in the vicinity of 0.84 in patients with heart failure. A splanchnic-to-large vessel hematocrit ratio of 0.91 has been observed in normal subjects.[24] Thus, depending on the large vessel hematocrit in any given case, the use of only a plasma tag will result in overestimation of splanchnic blood volume of approximately 8 per cent in the failure cases and around 4 per cent in the normal persons. The differences in splanchnic blood volume observed in this study are considerably greater than this, and differences between large vessel and splanchnic bed hematocrit are thought to play no significant role in the results obtained.

The possibility exists that the blood samples for T-1824 concentration obtained with the catheter from one of the hepatic veins are not representative of the T-1824 concentration of blood simultaneously emerging from other areas of the liver. The same theoretic objection applies to the measurement of hepatic blood flow by the bromsulphalein technic. The random use of different branches of the right hepatic vein in both patients and control subjects might produce some variation in results in any individual case; however, it seems unlikely that sampling variation in itself could be responsible for the significant mean increase in splanchnic blood volume observed in the congestive heart failure patients compared to the control group.

This increase in splanchnic blood volume in the congestive heart failure cases is even more strikingly reflected in terms of the average of the mean transit times across the splanchnic bed. Mean transit time calculated by dividing the splanchnic volume by the respective splanchnic flow averaged 85.6 seconds for the failure population as contrasted to 36.9 seconds for the normal group.

The average increase in splanchnic blood volume exceeded that observed in total blood volume. The mean ratio of splanchnic blood volume to total blood volume averaged 20.8 per cent in the normal controls, a value similar to that found by others.[25] This ratio was increased to 26.5 per cent in the patients with congestive heart failure. Thus, the splanchnic bed as well as the heart and lungs contributes to the increased total blood volume seen in congestive heart failure. The data imply that the splanchnic bed is relatively more distensible than other comparable venous beds, accepting a proportionally greater volume of blood in response to the same common elevated central venous pressure. This is not meant to infer that augmented venomotor tone, generally regarded as largely responsible for the increased venous pressure in congestive heart failure,[26] does not involve the splanchnic bed. However, the demonstration that there is more than a 50 per cent mean increase in the amount of blood normally present in the splanchnic bed in congestive failure, or a volume out of proportion to the increase in total blood volume, makes it reasonable to assume that the increased volume within the splanchnic bed plays an important role in maintaining the venous hypertension of this bed, irrespective of whether or not increased venomotor tone is present.

Anatomic studies suggest that the bulk of the splanchnic blood volume is contained within the hepatic and portal venous systems.[27] If one views the splanchnic reservoir as a passive elastic container, one expects the volume contained within to vary, within wide limits, as a function of the distending venous pressure.[28] Table 1 lists the values observed for right atrial mean and wedged hepatic vein pressures in these cases. The pressure gradient between the wedged and free hepatic vein positions did not exceed 2 mm. Hg in

any subject. Four of the patients (G.C., H.F., G.K. and E.S.) had atrial and portal venous pressures (as estimated by the hepatic vein wedge technic) within the normal range. Although still edematous at the time of study, these patients had responded to therapy with considerable diuresis and a reduction of venous pressure into the normal range. In these patients with normal intrahepatic sinusoidal and portal vein pressures, no significant increase in the volume of blood within the splanchnic bed was observed. The significant correlation of relatively moderate degree noted between wedged hepatic venous pressure and the splanchnic blood volume ($r = +.64$, $p < .05$) suggests that the amount of blood contained within the splanchnic bed in congestive heart failure is intimately associated with the level of the distending venous pressure.

Summary

The splanchnic blood volume was measured in 12 patients with congestive heart failure, and the results were compared with 10 normal persons.

Although splanchnic blood flow may be reduced in congestive failure, splanchnic blood volume is consistently increased. The splanchnic bed acts as a major reservoir for the increased total blood volume observed in these patients.

It is suggested that the enlarged splanchnic reservoir observed in congestive failure is an important factor in maintaining the venous hypertension of this bed.

Summario in Interlingua

Le volumine de sanguine splanchnic esseva mesurate in 12 patientes con congestive disfallimento cardiac. Le resultatos esseva comparate con illos obtenite in 10 casos normal.

Ben que le fluxo del sanguine splanchnic es reducite congestive disfallimento cardiac, su volumine es uniformemente augmentate. Le vasculatura splanchnic age como un major reservoir pro le augmentate volumine total de sanguine que es observate in iste patientes.

Es suggerite que le allargate reservoir splanchnic observate in disfallimento congestive es un factor importante in mantener le hypertension de iste vasculatura.

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A physician may possess the science of Harvey and the art of Sydenham, and yet there may be lacking in him those finer qualities of heart and head which count for so much in life.—*British Medicine in Greater Britain.* Montreal Med. Journal, 1897.

Results of Surgery for Congenital Pulmonary Stenosis

Comparison of the Transventricular and Transarterial Approaches

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Clinical and physiologic data before and after operation are presented in 25 patients who underwent surgical correction of congenital pulmonary stenosis with intact ventricular septum. Sixteen patients were operated on by the transventricular approach, 7 by the transarterial route, and 2 had infundibulectomies. Postoperative changes in the clinical status, phonocardiogram, electrocardiogram, x-rays, and right heart catheterization values are discussed. Comparison is made of the 2 major operative technics both in the present group and in cases gathered from a review of the literature.

CONGENITAL isolated pulmonary stenosis, variously called "pure" stenosis, stenosis with intact ventricular septum, and stenosis with normal aortic root, is no longer considered a rare anomaly.

At the present time there is little agreement concerning the various surgical methods for relief of pulmonary stenosis. Three approaches, Brock's transventricular "blind" method,[1] Söndergaard's[2] transarterial method, and Swan's[3] "open" transarterial approach with hypothermia are now generally in use. The last procedure has of necessity found less application because of the hitherto imperfect development of the corollary procedures of hypothermia and artificial circulation. Conflicting reports regarding the efficacy and relative merits of the various methods have appeared.[4, 5] A total of 134 patient reports have appeared in which cardiac catheterization was carried out, both before and after operation.[4-16]

This paper is concerned with the general picture of pulmonary stenosis and its response to intervention surgically by the 3 operative technics. From this clinic 25 patients have undergone surgery and postoperative catheterization and are reported here.

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MATERIAL AND METHODS

Since the introduction of cardiac catheterization in this clinic in 1951, a total of 72 patients have had a diagnosis of pulmonary stenosis with intact ventricular septum verified by cardiac catheterization and angiocardiography or surgery.[17] Of these the defect has been definitely of the pure valvular type in 53, purely infundibular in 10, combined in 3, and in 6 cases no angiocardiography or surgery was performed to establish the anatomic lesion definitely. Twenty-eight patients have been operated on for relief of stenosis.

In selecting patients for operation a right ventricular systolic pressure of 75 mm. Hg at peak systole has generally been considered the boundary line separating the mild and the moderate-to-severe types of stenosis, patients with higher levels evidencing either marked clinical impairment of physical capacity, marked electrocardiographic evidence of right ventricular hypertrophy and strain, or both. In the present series 4 patients (cases 1, 6, 15, 20) were considered to be in cardiac decompensation and incapacitated at the time of operation, and over half of all patients had a definite decrease in exercise tolerance by history. Seven patients were found at catheterization to have a patent foramen ovale permitting catheter passage to the left heart and in 4 cases resulting in oxygen desaturation via a right-to-left shunt. One patient (case 12) had a definite atrial septal defect with left-to-right shunt, this defect being repaired at the time of the operation for the stenosis. Two patients (cases 13, 22) had evidence of a patent ductus arteriosus, both of these also being closed at the time of operation (table 1). Two patients died shortly after op-ra-

tion and 1 patient was not available for postoperative examination. The remaining 25 patients form the basis of this report.

The group comprises 16 males and 9 females ranging in age from 11 months to 17 years (average 5 years, 10 months) at the time of operation. Postoperative examination was carried out 1 to 36 months (average 19 months) following operation, and consisted of identical procedures used preoperatively, namely, routine clinical examination, electrocardiogram, phonocardiogram, standard chest x-rays, and right heart catheterization. Selective angiocardiography was carried out in 24 patients before operation and in 10 patients postoperatively.

Electrocardiography. Tracings were taken on an Elmqvist 6-channel photographic recording apparatus.* Standard, unipolar extremity, and chest leads including V_{3R} and V_7 were taken in all cases. A paper speed of 40 mm. per second was used. Electric axis was calculated by measuring the wave amplitudes in leads I and III rather than by the more time-consuming planimeter method. Criteria used for the diagnosis of right ventricular hypertrophy consisted of standards established in the literature as suited to this particular age group.[18-22] In those cases with V_1 complexes of the rsR′ type, hypertrophy was diagnosed if the R′ wave exceeded 10 mm. and other substantiating signs were present. Large, peaked P waves over the right precordium were interpreted as a sign of right atrial enlargement as well as an indirect sign of right ventricular hypertrophy.

Calibrated Phonocardiography. Recordings were made on an Elema apparatus connected to the 6-channel electrocardiograph. The phonocardiograph, constructed with modifications according to principles outlined by Mannheimer,[23] contained 6 filters having the nominal frequencies of 25, 50, 100, 200, and 400 c.p.s. plus a filter giving "earlike" tracings. A simultaneous electrocardiogram was always recorded, and a built-in device insured constant sensitivity of the apparatus. By this feature reproducible amplifications were obtained and hence "calibrated" recordings. The microphone was of the "dynamic" type. Paper speed was 100 mm. per second in all recordings. Tracings were taken in most instances over the second, third, and fourth left intercostal spaces, second right intercostal space, and over the apex, the patient being in the supine position and holding the breath if possible. Tracings were analyzed before and after operation for the time of onset of the first sound and its amplitude; the occurrence of a "systolic click"; onset, intensity, position, form, and endpoint of the systolic murmur; splitting of the second sound; amplitude of the pulmonary component of the second sound; and occurrence, position, and character of diastolic murmurs.

Roentgenography. Radiographic examination, including standard posteroanterior, right and left lateral, oblique, and barium swallow films were taken on all patients. Heart volumes were calculated according to the method of Rohrer and Kahlstorf and correlated to the body surface area, expressed in ml. per $M.^2$. The normal values for the respective age groups were taken from Carlgren and Eek,[24] Kjellberg et al.,[25] and Lind.[26]

Angiocardiography was of the "selective" type, injection being made with the tip of the catheter placed in the right ventricle. Injection of the contrast material was accomplished by means of an automatic injector apparatus manufactured according to Gidlund's principle. The radiographic apparatus was of the rapid-change, bi-plane type, capable of taking 12 exposures per second in each plane.* The injection material used was either Urokon sodium (sodium acetrizoate) 70 per cent, or Rheopaque (sodium 3-acetyl amino-2, 4, 6-triiodobenz) the dosage calculated according to the patient's weight, the size of the catheter, and the pulse frequency.

Catheterization. Right heart catheterization was carried out in the usual manner,[17] and oxygen saturations were determined by the Brinkman Hemoreflector** checked by Van Slyke's method.

Surgical Procedures. Three types of operation were used: 16 patients were operated on by the Brock transventricular approach and comprise group A of this report; 7 patients were operated on by the transpulmonary artery method—5 of these according to Söndergaard and 2 with the use of artificial circulation; these 7 patients make up group B. Two patients were operated on for relief of an isolated infundibular stenosis by infundibulectomy, 1 each by transventricular and open approach, and comprise group C.

Results

Two of the total of 28 patients died, giving an over-all mortality in the series of 7 per cent, being 11 per cent for the Brock method and 0 per cent for the transarterial approach. One patient was not available for catheterization after surgery. Clinically, the remaining

*Manufactured by Elema AB, Stockholm, Sweden.

**Manufactured by Kipp, Delft, Holland.

TABLE 1.—*Right Heart Catheterization Results**

Case no.	Age	Sex	Months Postop.	R V P		P A P		Gradient		O_2 Art. Sat. (%)		Ass. defect
				Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	
Group A. Transventricular valvulotomy												
1	8	M	24	230/0	70/8	16/3	21/5	214	49	97	94	
2	7	M	36	220/–	120/6	15/–	20/5	205	100	—	95	
3	4	M	17	198/3	40/11	11/8	22/8	187	18	97	98	FO
4	6	M	6	195/11	80/12	12/6	16/8	183	64	97	98	
5	4	M	25	170/10	35/1	14/7	16/6	156	19	92	98	FO
6	2	F	15	155/13	18/6	—	—	—	—	73	84	FO
7	10	F	7	151/14	37/10	12/6	22/5	139	15	86	96	
8	10	F	33	136/3	40/10	12/9	20/6	124	20	86	—	FO
9	10	M	21	135/12	40/9	19/8	23/5	116	17	—	98	
10	2	F	32	110/0	31/0	10/0	20/4	100	11	97	99	
11	14	M	25	108/12	40/12	12/6	26/4	96	14	96	97	
12	14	M	4	95/9	31/3	14/8	18/8	81	13	90	95	ASD
13	11	F	24	90/4	53/10	26/9	23/7	64	30	—	96	PDA
14	14	M	15	85/7	61/0	14/6	17/7	71	44	—	96	
15	3	F	12	85/6	35/4	—	22/2	—	13	—	—	
16	9	M	24	70/0	28/3	15/9	11/7	55	17	—	98	
Avg.	8	—	20	140/7	47/7	14/7	20/6	128	31			
Group B. Transarterial valvulotomy												
17	6	F	1	163/3	34/5	10/4	19/7	153	15	88	91	FO
18	17	F	12	160/0	115/10	—	18/8	—	97	89	99	FO
19	7	M	4	115/11	35/5	15/9	16/6	100	23	—	—	
20	1	M	7	107/9	89/7	—	20/5	—	69	99	—	FO
21	13	M	19	97/13	25/12	25/8	21/7	72	4	98	—	
22	17	F	19	82/10	40/4	50/10	28/7	33	12	96	—	PDA
23	7	M	9	80/6	41/8	20/10	30/4	60	11	—	98	
Avg.	9	—	10	115/8	54/7	24/8	21/6	84	13			
Group C. Infundibulectomy												
24	7	M	11	152/0	122/7	15/5	16/9	137	106	93	—	FO
25	17	M	13	133/6	25/1	15/5	18/3	118	7	98	98	
Avg.	12	—	12	143/3	74/4	15/5	17/6	128	57			

* RVP, right ventricular pressure, mm. Hg; PAP, pulmonary artery pressure, mm. Hg; Gradient, systolic pressure difference between right ventricle and pulmonary artery, mm. Hg; FO, foramen ovale; PDA, patent ductus arteriosus; ASD, atrial septal defect.

25 patients all evidenced improvement following surgery regardless of the degree of lowering of right ventricular systolic pressure. This improvement was manifested by increase in exercise capacity, although no ergometer tests are available in a sufficient number of cases for comparison of working capacities before and after operation.

Hemodynamically, the average right ventricular pressure in group A was reduced 93 mm. Hg and in group B was reduced 61 mm. Hg (table 1). The difference between the 2 preoperative values (25 ± 18.2 mm. Hg) was not statistically significant ($p > 0.05$), nor was the postoperative difference (7 ± 14.3 mm. Hg) significant. Of the 2 cases of infundibulectomy the pressure in the one operated on with open heart technic became normal.

The right ventricular-pulmonary artery pressure gradient in group A was reduced 97 mm. Hg or 76 per cent, while corresponding values in group B gave a 71 mm. average reduction, or 85 per cent. Systolic pulmonary artery pressures in group A increased significantly ($p < 0.01$) postoperatively from a preoperative average of 14 mm. to 20 mm. In

group B the average systolic pulmonary artery pressures *decreased* postoperatively from 2- mm. to 21 mm. Patient no. 22, having a p- operative pulmonary artery pressure of 5(10, accounts for this difference (table 1). A giocardiography and surgery revealed this h pertension to be on the basis of a pericardi l narrowing of the main pulmonary artery, w ich was relieved at operation. If this pati t is not included in calculation for group B the results then show an average increase postoperatively from 19 mm. to 21 mm., but this difference is not statistically significant ($p > 0.05$).

Eleven of the 16 patients in group A had good operative results as evidenced by postoperative right ventricular pressure levels of 40 mm. or below and a right ventricular-pulmonary artery pressure gradient of 20 mm. or less. Five of the 7 patients in group B had comparable results. Two patients in both group A and B plus 1 with infundibulectomy had poor operative results with residual right ventricular pressures of 80 mm. or above. Three patients, all of group A, are considered to represent a fair result with postoperative pressures between 60 and 80 mm.

Arterial oxygen saturation (table 1) showed a definite tendency toward return to normal values. Following operation, those 5 patients with patent foramen ovale and low oxygen saturation plus the one patient with atrial septal defect all evidenced significant increase in saturation values after reduction of right ventricular pressure toward normal.

Results of operations by the transventricular and transarterial methods in the 23 patients of group A and B were compared statistically to determine whether any significant difference existed in these results or whether the operative results were in any possible way dependent on the preoperative right ventricular pressure (table 2). No statistical difference ($p > 0.05$) was found. No statistical correlation was found before and after surgery between the individual pressures ($r = 0.432$, $p > 0.05$ for group A, and $r = 0.421$, $p > 0.05$ for group B, and $r = 0.355$ for the whole material); thus no comparison could be made of the 2 methods.

TABLE 2.—*Combined Results from Literature of Valvulotomy for Pulmonary Stenosis (Patients with Preoperative and Postoperative Catheterization)*

Author	Cases	Right ventricular systolic pressure (mm. Hg)		Difference (mm.Hg)	Mortality (%)
		Preop.	Postop.		
Transventricular valvulotomy					
Galligan 1952	2	179	59	120	—
Lurie 1953	7	100	78	22	—
Kirklin 1953	2	125	52	73	16
Bing 1954	8	127	92	35	—
Soulie 1954	9	171	108	63	—
Humphreys 1954	3	193	75	118	—
Blount 1954	5	168	65	103	10
Campbell 1955	18	142	61	81	14
Silverman 1956	6	188	52	135	14
Lillehei 1956	20	116	56	60	—
Hosier 1956	17	146	78	68	8
Average		142	71	71	
Present Series	16	140	47	93	11
Transarterial valvulotomy					
Blount 1957	25	135	44	91	5
Derra 1957	12	171	61	110	—
Present Series	7	115	54	61	0
Average	44	142	50	92	

Phonocardiographically (table 3) the first sound was considered within normal limits in all but 1 case with regard to its time of onset after the Q wave of the electrocardiogram and with regard to its duration. Average time of onset was 0.05 second following beginning of the Q wave both before and after operation. The point of maximum intensity of the first sound, with very few exceptions, was found in the fourth left intercostal space or less frequently over the apex. In 6 instances preoperatively the amplitude of the first sound was markedly less than normal. Postoperatively these amplitudes returned to normal in 4 of the 6 cases. No correlation of amplitude with the degree of right ventricular hypertension or lack thereof could be established. In only 2 instances was there definite splitting of the first sound into easily recognizable tricuspid and mitral components. Postoperative split-

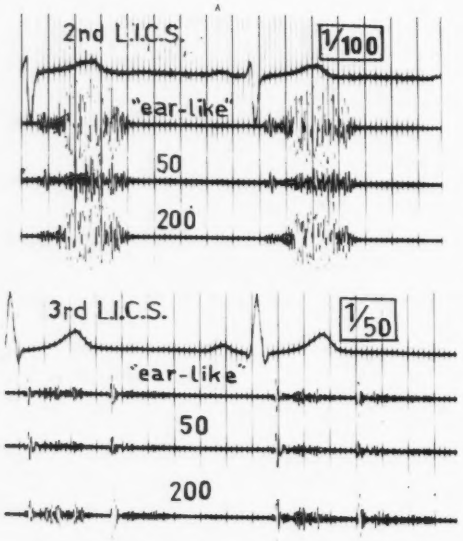

FIG. 1. Phonocardiograms in case 11 preoperatively and postoperatively. *Top,* large diamond-shaped, late systolic murmur before surgery with absence of pulmonic component of second sound. *Bottom,* postoperative systolic murmur appears early in systole and is of physiologic type. Pulmonary component of second sound now visible. Appearance of protodiastolic insufficiency murmur. *Boxed figures* denote degree of amplification, *other figures* represent standard filter frequencies. Time interval is 0.10 second between *heavy lines. 2nd and 3rd L.I.C.S.* denote second and third left intercostal spaces respectively.

ting was seen in 6 instances, maximum splitting being 0.03 second.

Contrary to the experience of Leatham[27, 28] a systolic click was seen in only 2 tracings of the total of 48 recordings. Despite the supposed prerequisites of marked pulmonary artery dilatation and relatively low right ventricular pressure in many instances, this sound was not a common finding in this series.

Preoperatively all patients of groups A and B in whom tracings were available for study showed the typical "stenosis murmur" consisting of a diamond-shaped murmur with peak in either midsystole or late systole (fig. 1). Maximum intensity of the murmur was over the second left intercostal space in the majority, but was occasionally seen to be in the third left intercostal space. Characteristically this murmur began immediately or very soon after the end of the first sound and often extended past the aortic component of the second sound. Postoperatively it was seen to change both in position and character. In 22 of the 23 cases comprising groups A and B, the murmur came to occupy a position in early or midsystole after operation. In the case in which the murmur retained its late systolic position (patient 18), the operative result was classified as poor. In 12 instances the murmur changed form to that of a low amplitude, low-frequency murmur of the physiologic type. In the remaining 11 cases it retained its diamond shape and was of an amplitude greater than that seen in a physiologic murmur. However, in those cases with good operative result the murmur, although still diamond shaped, was one of low frequency. In only 4 of these 11 patients was the postoperative right ventricular pressure 40 mm. or below, whereas only 1 of the postoperative physiologic murmurs was associated with a right ventricular pressure of 40 mm. or above. Related to the right ventricle-pulmonary artery gradient, only 1 of the 11 physiologic murmurs occurred in a patient with a gradient greater than 20 mm. Of the 11 diamond-shaped postoperative murmurs 5 were associated with gradients less than 20 mm. but angiocardiography showed residual "dome" shape or narrowing of the valvular orifice in 3 of these 5 after operation.

In 11 of 23 patients the second sound on the preoperative phonocardiogram was interpreted as being single, with absence of the pulmonary component. In general this finding was associated with high right ventricular pressures (above 135 mm.) and a high degree of stenosis, although the sound was also single in 3 cases with pressures at the 85 mm. level. Conversely, only 2 cases with right ventricular pressure greater than 135 mm. showed a definite pulmonary component of the second sound, and in both these instances the splitting of the aortic and pulmonary component was marked (0.08-0.09 second). The remaining patients demonstrated splitting of the second sound ranging from a normal interval of 0.04 second (2 cases) to 0.10 second. The

TABLE 3.—*Phonocardiographic Analyses**

Case No.	Preoperative				Postoperative				
	Pressure		Murmur	Splitting 2nd sound	Pressure		Murmurs		Splitting 2nd sound
	RV*	PA	Systolic	(sec.)	RV	PA	Systolic	Diastolic	(sec.)
Group A									
1	230/0	16/3	LS	single	70/8	21/5	MS – D	–	single
2	220/–	15/–	—	single	120/6	20/5	MS – D	–	0.06
3	198/3	11/8	LS	0.09	40/11	22/8	ES – D	PD	0.04
4	195/11	12/6	MS	single	80/12	16/8	MS – D	–	single
5	170/10	14/7	LS	0.08	35/1	16/6	ES – D	PD	0.06
6	155/14	——	LS	single	18/6	——	ES – P	–	single
7	151/14	12/6	LS	single	37/10	22/5	ES – P	PD	0.08
8	136/3	12/9	LS	single	40/10	20/6	ES – D	–	0.04
9	135/16	19/8	LS	0.08	40/9	23/5	ES – P	PD	0.04
10	110/0	10/0	LS	0.04	31/0	20/4	ES – P	PD	0.04
11	108/12	12/6	LS	0.10	40/12	26/4	ES – P	PD	0.06
12	95/9	14/8	LS	0.10	31/3	18/8	ES – P	MD	0.04
13	90/4	26/9	MS	0.05	53/10	23/7	ES – P	–	0.05
14	85/7	14/6	—	single	61/0	17/7	MS – D	–	0.08
15	85/6	——	LS	single	35/4	22/2	ES – P	PD	0.06
16	70/0	15/9	LS	0.06	28/3	11/7	ES – P	–	0.06
Group B									
17	163/3	10/4	LS	single	34/5	19/7	ES – P	–	single
18	160/0	——	LS	single	115/10	18/8	LS – D	–	single
19	115/11	15/9	MS	0.08	35/5	16/6	MS – D	–	0.05
20	107/9	——	LS	0.04	89/7	20/5	MS – D	–	0.04
21	97/14	25/8	LS	0.09	25/12	21/7	ES – P	PD	0.07
22	82/13	50/10	MS	single	40/4	28/7	ES – P	–	0.04
23	80/6	20/10	MS	0.07	41/8	30/4	ES – D	PD	0.06
Group C									
24	152/0	15/5	LS	single	122/7	16/9	ES – D	–	0.08
25	133/6	15/5	LS	single	25/1	18/3	ES – P	–	0.05

*RV, right ventricle; PA, pulmonary artery; ES, early systolic; MS, midsystolic; LS, late systolic; D, diamond-shaped; P, physiological; Single, no pulmonary component seen; PD, protodiastolic.

great majority of the visible pulmonary components were of markedly reduced amplitude. The 2 patients with infundibular stenosis both exhibited a single second sound preoperatively.

Postoperatively a definite trend toward normalization of the second sound was observed. In only 5 instances did a preoperatively single sound persist as such after operation, and but 2 of these were in connection with good operative reduction of the right ventricular pressure. Seven phonocardiograms previously lacking a pulmonary sound registered this sound following adequate reduction of right ventricular pressure, and in 4 other tracings the amplitude of this component increased.

None of the 25 patients exhibited a diastolic murmur in the preoperative phonocardiograph. Postoperatively a clinically and phonocardiographically easily detectable murmur developed in 8 patients operated on by the Brock technic and in 2 patients operated on by the transarterial method. Nine of the diastolic murmurs that developed were of the typical protodiastolic insufficiency type. In each instance appearance of the murmur was associated with a good operative result. Six of the 10 murmurs existed with a diastolic pressure in the pulmonary artery of 5 mm. or less.

Electrocardiography. Twenty of the 25 preoperative records (table 4) showed patho-

TABLE 4.—*Electrocardiographic Analyses**

Case no.	R V P		Elect. axis		R or R′ −V1		RV strain	
	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
Group A								
1	230/0	70/8	+ 95	+ 95	32	32	+	+
2	220/–	120/6	+120	+108	57	42	+	–
3	198/3	40/11	+130	+ 95	51	9	+	–
4	195/11	80/12	+120	+ 85	63	45	+	+
5	170/10	35/1	+128	+ 82	92	16	+	–
6	155/13	18/6	+ 96	+ 76	9	1	–	–
7	151/14	37/10	+178	+140	90	25	RBBB	RBBB
8	136/3	40/10	−148	+180	10	5	–	–
9	135/12	40/9	+120	+ 80	21	7	+	–
10	110/0	31/0	+126	+122	29	9	–	–
11	108/12	40/12	+120	+100	28	8	–	–
12	95/9	31/3	+125	+ 10	15	9	–	–
13	90/4	53/10	+ 85	+ 82	22	4	–	–
14	85/7	61/0	+ 95	+112	5	22	–	RBBB
15	85/6	35/4	+1 5	+ 60	40	5	+	–
16	70/0	28/3	+108	+ 92	9	8	–	–
Avg.	140/7	47/7	+122	+ 95	35	16	–	–
Group B								
17	163/3	34/5	+128	+118	33	30	+	+
18	160/0	115/10	+166	+170	21	10	–	–
19	115/11	35/5	+116	+ 95	32	25	–	–
20	107/9	89/7	+120	+120	75	52	+	+
21	97/13	25/12	−120	− 50	17	7	–	–
22	82/10	40/4	+128	+ 92	15	5	–	–
23	80/6	41/8	+ 96	+ 92	26	14	–	–
Avg.	115/8	54/7	+125	+105	31	21	–	–
Group C								
24	152/0	122/7	+115	+112	52	60	+	+
25	133/6	25/1	+112	+ 93	42	21	+	RBBB
Avg.	143/3	74/4	+113	+102	47	40	–	–

*RVP, right ventricular pressure, mm. Hg; R or R′−V_1, height of R or R′ wave, mm. in lead V_1; RV Strain, right ventricular strain; RBBB, complete right bundle-branch block.

logic deviation of the electric axis, which was marked right axis deviation in 18 and left axis deviation in 2. The average axis for the other 23 patients was +122 degrees. Postoperatively a statistically significant reduction ($p < 0.01$) in degree of axis deviation was observed, the large majority returning to normal values. No correlation between right ventricular pressure and degree of axis deviation preoperatively could be demonstrated ($r = 0.121$, $p > 0.05$), but a probably significant correlation ($r = 0.458$, $p < 0.05$) was found postoperatively. When preoperative and postoperative data were taken together, a highly significant ($p < 0.001$) but low correlation ($r = 0.469$) was found.

Right ventricular hypertrophy was diagnosed preoperatively in 22 cases by electrocardiogram. Right ventricular strain, as evidenced by marked ST-segment depression and T-wave inversion in the right precordial leads, was diagnosed in 7 records of group A and in 2 records of group B. One patient (no. 7) had a complete right bundle-branch block prior to operation. Following surgery signs of right ventricular hypertrophy disappeared in 9 of 22 cases as evidenced by marked reduction in the size of the R or R′ wave in lead V_1, an average reduction from 35 mm. to 1[illegible] mm. of high statistical significance taking place in groups A and B. With only 1 exception, this regression of electrocardiographi[illegible]

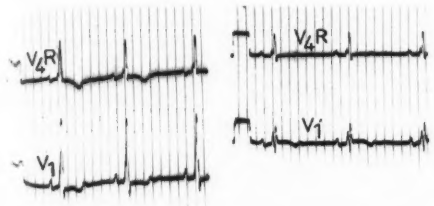

FIG. 2. Preoperative and postoperative electrocardiographic leads V_1R and V_1 in case 11. *Left*, prior to surgery large R waves indicative of right ventricular hypertrophy. *Right*, postoperative reduction of R-wave size with appearance of rsR′ pattern. Time interval between *heavy lines*, 0.10 second.

hypertrophy occurred after right ventricular pressure was lowered to 40 mm. or less.

An attempt at correlation of the height of the R or R′ wave in V_1 with the right ventricular pressure showed that preoperatively there was probably significant ($r = 0.483$, $p < 0.05$) correlation between these variables. This correlation was increased after operation ($r = 0.693$) and became highly significant ($p < 0.001$). Covariance analysis showed no significant difference between the regression equations of R-V_1 plotted against the right ventricular pressure before and after operation. Thus, the relationship between right ventricular pressure and R-V_1 was not shown to change significantly by operation.

As has been observed in other series,[4] the electrocardiograms of 8 of our patients showed postoperative changes in V_1 consisting of development of an rSR′ complex, whereas the preoperative complex had a tall R wave (fig. 2). Two of these patterns were definitely on the basis of right bundle-branch block (both group A), but the remaining 6 were in the group in which no signs of right ventricular hypertrophy could be detected. No direct correlation of emergence of this pattern with right ventricular pressure changes or pressure gradient changes could be established.

Correlative signs of right ventricular hypertrophy also evidenced regression toward normal values following operation. Abnormally large P waves showed return to normal values in 10 of 18 cases. Six electrocardiographic records showed return of the transitional zone to normal position in the chest leads. Signs of ventricular strain disappeared in 6 of 9 tracings.

Radiologic Results. Heart volumes for the total of 25 patients decreased highly significantly following surgery (table 5) from an average of 390 ml. per M.^{2}, which is at the upper limits of normal, to 330 ml. per M.^{2}. Although many of the heart volume figures preoperatively were at the upper limits of normal, 6 patients showed marked pathologic cardiac enlargement (cases 1, 2, 10, 20, 24, 25). These latter patients showed uniform reduction to normal levels, and indeed, even the moderately enlarged or "normal"-sized hearts

TABLE 5.—*Radiologic Examinations**

Case no.	Heart vol. (ml./m^2)		Post-stenotic dil.		Ostium size (mm.)	
	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
1	540	290	Mod.	—	2–3	—
2	490	350	—	Mod.	—	No dome
3	340	220	Sl.	Sl.	5	Dome
4	420	300	Mod.	—	7	—
5	340	300	Mod.	Mod.	2	14 No dome
6	320	350	Mod.	—	2–3	—
7	400	350	Sl.	—	3	—
8	270	330	Mod.	Mod.	2	10 No dome
9	390	400	Mod.	Sl.	8	15 Dome
10	590	400	Mod.	—	3–4	—
11	380	370	Marked	Less	5	No dome
12	350	330	Mod.	—	8–9	—
13	340	340	Sl.	—	7	—
14	280	315	Mod.	—	10	—
15	450	350	None	None	6	No dome
16	390	300	Sl.	—	7	—
Avg.	390	330				
17	290	240	Mod.	Less	5	No dome
18	390	370	Mod.	—	Small	—
19	290	290	Marked	—	Not seen	—
20	510	370	Sl.	Less	2–3	5 Dome
21	320	290	Mod.	Mod.	8	11 No dome
22	240	250	Mod.	—	11	—
23	330	310	Mod.	—	5	—
Avg.	340	300				
24	600	450	Sl.	—	—	—
25	540	340	None	—	—	—
Avg.	570	395				

* Post-stenotic dil., post-stenotic dilatation of pulmonary artery; Mod., moderate; Sl., slight.

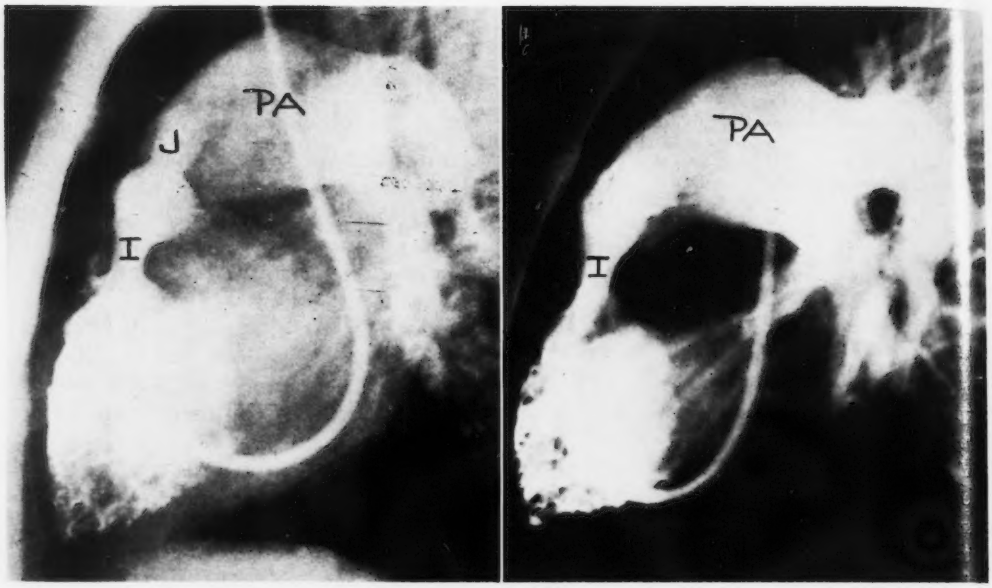

FIG. 3. Case 11. *Left*, preoperative dome formation of pulmonary valve with eccentric "jet" of blood through ostium. *Right*, postoperatively no valvular dome seen, but residual pulmonary artery dilatation 25 months after operation. Good operative result. *I*, infundibulum; *J*, jet; *PA*, pulmonary artery.

returned to more normal size and contour postoperatively.

Right ventricular hypertrophy, associated with increased trabeculations of the right ventricle and moderate-to-marked thickening of the right ventricular wall, was seen in 23 of 24 preoperative angiocardiographies. These signs regressed in all 9 patients who had postoperative examinations.

In those cases that evidenced "dome" formation of the valves prior to surgery, ostium size varied from 2 to 11 mm. In 6 patients the dome has completely disappeared postoperatively (fig. 3). Evidence of residual dome formation was seen in 3 cases, but in 1 the ostium size was estimated at 15 mm. compared with 8 mm. preoperatively (fig. 4). In these 9 reexaminations, signs of post-stenotic dilatation of the pulmonary artery decreased in 4 patients, of which 3 had good operative results, and remained unchanged or slightly increased in 4, all of which had good results. In 1 patient no dilatation was seen either before or after surgery.

Signs of regurgitation through the pulmonary valve after valvulotomy appeared in 5 instances in those patients with postoperative angiocardiography. In 4 of these the radiologic sign was associated with a definite clinical and phonocardiographic diastolic murmur.

Pulmonary vascularity, often markedly decreased prior to surgery, showed a tendency to increase following operative intervention, but no exact evaluation of this change could be made.

DISCUSSION

The mortality figures in the present series of 28 operated patients cannot be taken as conclusive of a definite difference in the operative methods used, since one patient exhibited the most extreme cardiac failure seen in the series, and the other, a patient who had an associated large atrial septal defect that had not been diagnosed preoperatively, died dur-

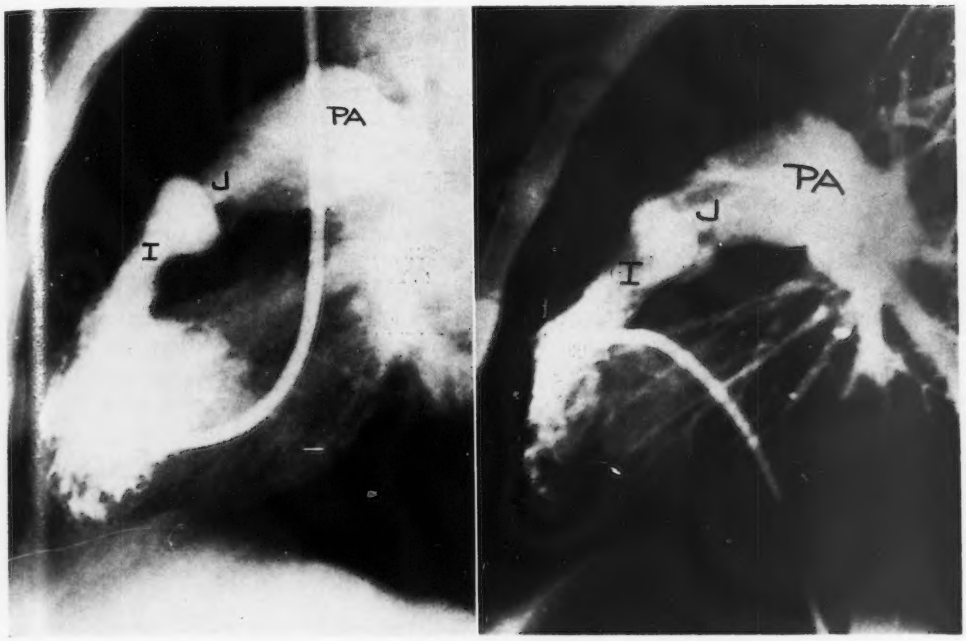

FIG. 4. Case 9. *Left*, preoperatively valvular dome with jet. *Right*, residual dome formation of valves postoperatively, ostium size ca. 15 mm., but good operative result. *I*, infundibulum; *J*, jet; PA, pulmonary artery.

ing the second operative procedure performed here.

The remaining 25 patients have all evidenced improvement in exercise capacity, many being able to resume perfectly normal activity. That this improvement also occurred in those patients whose postoperative right ventricular pressure levels remained high, is an unexplained phenomenon. This clinical improvement in the face of less-than-ideal operative results has been observed in other series as well as in studies on the operative results for the relief of mitral stenosis and coronary insufficiency. A factor often mentioned as possibly playing a role in this improvement is the subjective influence that is so difficult to evaluate. Due to the very young age of many of our patients, we do not believe that this is such an important contribution to improvement in this group.

Investigation of changes before and after operation in A-V oxygen differences showed no definite basis for supposing that a decrease in this value, despite continued right ventricular hypertension, might be the explanation. Likewise, review of the degree of increase in pulmonary artery pressure and arterial oxygen saturation in these patients postoperatively fails to substantiate the supposition that these factors might account for the improvement. Increase in pulmonary flow, cannot be evaluated in this series, since no cardiac outputs were determined. This finding, however, might well account for some degree of clinical improvement.

The clinical examinations by phonocardiography and electrocardiography showed definite and significant changes after surgical intervention. The late, diamond-shaped murmur was seen to change form and position, becoming either an early-systolic physiologic murmur or a low-frequency, small, diamond-shaped murmur after successful relief of the valvular stenosis. Single second sounds lack-

ing a pulmonary component revealed a postoperative tendency to development of this component at lower right ventricular pressures, and sounds that were previously abnormally split with small pulmonary components evidenced decrease of the splitting interval and increase in the component's amplitude. These observations follow relief of the anatomic stenosis and shortening of the stenotically prolonged right ventricular systolic period. Increased mobility of the valve leaflets, as well as increased pulmonary artery pressure, undoubtedly form a basis for the reappearance or increased amplitude of the second sound's pulmonary component.

Postoperatively a diastolic murmur was heard and was seen on the phonocardiogram in 10 patients, 8 in group A and 2 in group B. In our experience development of this short, low-amplitude protodiastolic murmur is a reliable sign of good operative right ventricular pressure reduction, although not an invariable accompaniment of it. We believe this murmur to be a result of the pressure differential in early diastole between the higher level in the pulmonary artery and the comparatively low right ventricular level. As the latter gradually rises to a higher middiastolic level, it thus prevents a significant regurgitation such as occurs in aortic valve disease. As has been expressed by other authors,[4] we have no evidence now to regard this murmur as representative of a significant physiologic defect; on the contrary, because of the short regurgitant period we would not expect any marked right ventricular diastolic overloading. This view may be supported by the fact that heart volume decreased in all patients developing diastolic murmurs and continued outpatient follow-up has failed to show any recent increase in these volumes.

Our results showed no significant correlation either before or after operation between the right ventricular pressures and the associated degree of electric axis deviation. That an electric axis of +95 degrees existed in the presence of a right ventricular pressure of 230 mm. Hg while an axis of +155 degrees was related to a pressure of 85 mm. Hg is ample illustration of the unreliability of guessing the degree of right ventricular hypertension from the electric axis. Although individual pressure did not correlate with the degree of axis deviation, a significant overall postoperative reduction of right axis deviation in the entire material did occur.

Regarding the postoperative development of the rsR′ complex in V_1, results in the present series do not elucidate the etiology of this pattern. It is not clear to us why a so-called "incomplete right bundle-branch block" should develop postoperatively in these patients when the operative procedure does not necessarily involve structures near the right bundle. Whether this rsR′ pattern is representative of hypertrophy of the right ventricular outflow tract[29-35] or whether it is due to diastolic overloading of the ventricle according to Cabrera and Monroy,[36] we cannot now say.

Radiologic decrease in heart volume and improvement in the signs of right ventricular hypertrophy paralleled similar changes of the hemodynamic and electrocardiographic signs of disturbed right heart function. The significant decrease in heart volume in our material is at variance with some presented previously,[4, 7] but these latter measurements were on the basis of the cardiothoracic ratio. Abolishment of a valvular dome with a very small opening that had produced a powerful systolic jet of blood resulted in a decrease of the pulmonary artery's postvalvular width in only one half of the cases examined. Regression of this post-stenotic dilatation is not an immediate postoperative occurrence, and often requires years to recede fully. It can thus not be utilized as a reliable sign of operative success or failure as is emphasized by the fact that the dilatation remained unchanged in size or slightly increased in 4 instances all associated with good operative results. Those cases in which a valvular dome persisted after valvulotomy are discussed below in connection with poor operative results.

Those operative results that are classified as "poor" in 5 patients and "fair" in 3 deserve particular attention. Various reasons

for such failure to reduce right ventricular pressure to normal levels have been presented in the literature, and we have attempted to evaluate our 8 cases from different viewpoints in an attempt to explain the results.

The probability that a combined valvular-infundibular stenosis was present and the outflow tract narrowing undetected prior to surgery would seem to be very small in this group. Preoperative selective angiocardiography, carried out in all but 1 patient, and postoperative angiocardiography in 2 of those with poor results failed to show any suggestion of a concomitant infundibular stenosis. Although it is conceivable that a very high infundibular stenosis might be missed by too rapid withdrawal of the catheter, our pressure curves do not show any so-called "third ventricle" on the withdrawal recordings. At the time of operation finger exploration of the infundibular region has also failed to reveal any narrowing at this point.

Thick, fibrous valves might be thought to be resistant to adequate surgical manipulation and thus produce a poor result. However, 1 of our patients (case 8) was shown by angiocardiography and at operation to have this extremely thick type of valve, a fibroma-like growth being detected on 1 of the cusps. The result in this patient has been good, and postoperative angiocardiography reveals quite adequate valvular motion despite the extreme residual valvular thickness. It thus seems possible for even the thickest valves to be incised and well mobilized.

Another possible basis for a poor result is a re-fusion of the valves after a perfectly adequate valvulotomy. Again, angiocardiography has shown postoperative evidence of residual dome formation in 3 patients in whom a supposedly adequate valve fracture was performed and right ventricular pressure well lowered. Whether this represents valvular refusion or inadequacy of the initial fracture is impossible to say.

As previously mentioned, there have appeared conflicting reports as to efficacy and relative merits of the various surgical procedures devised for the correction of pulmonary stenosis.[4, 5] Our results did not show any significant difference in the efficacy of the transventricular and transarterial approaches when the hemodynamic findings were taken as a basis of comparison. Postoperatively both the systolic right ventricular pressure and the right ventricle-pulmonary artery gradient did not differ significantly in groups A and B.

In order to clarify further the comparison of the results obtained by these 2 methods calculations were performed on the basis of the results in those reports in the literature in which the patients' individual preoperative and postoperative hemodynamic data—and not only the mean value—were given. Such data suitable for statistical calculations were given for the transventricular approach of Lurie,[14] Soulié,[11] Blount,[9] Campbell,[5] Silverman,[8] Hosier,[7] and the present report, and for the transarterial method by Blount,[4] Derra,[16] and ourselves. In the 78 cases operated on by the transventricular approach the systolic right ventricular pressure decreased from a mean preoperative value of 147 ± 5.4 mm. Hg to 68 ± 3.9 mm. Hg postoperatively. The corresponding figures for the 44 cases in which the transarterial approach was utilized were 142 ± 7.0 mm. Hg and 50 ± 4.3 mm. Hg.

Thus, although the preoperative level of the systolic pressure did not differ significantly in these 2 groups (difference 5 ± 8.9, $p > 0.05$), there was a significant difference in the postoperative values. The mean systolic pressure was lower by 18 ± 5.8 mm. Hg ($p < 0.01$) in the group operated on by the transarterial approach. These findings can be taken as showing that the transarterial method gives better results.

When the data reported by the different groups were taken together there was a highly significant ($p < 0.001$) although low correlation between the preoperative and postoperative systolic right ventricular pressure. The coefficients of correlation were 0.375 for the transventricular approach, 0.505 for the transarterial, and 0.412 for the whole material.

This correlation between the right ventricular pressures before and after operation

shows that the selection of the time for operation might be of more importance than the operative technic employed, and that ideal results might not be uniformly obtained by any method in cases with severe and prolonged right ventricular hypertension. Careful catheterization and recording of pressure curves, and experienced angiocardiographic interpretation, combined with adequate valvulotomy, should reduce the incidence of unfavorable results to a minimum.

Summary

The clinical and physiologic results of surgery for the relief of pulmonary stenosis in 25 patients are presented. Sixteen patients were operated on by the transventricular method and 7 by the transarterial; in addition 2 infundibulectomies were performed.

Operative mortality was 7 per cent for all operations. Clinical improvement was uniformly good, regardless of the operative results.

Significant improvement in abnormal deviation of the electric axis and right ventricular hypertrophy were seen in the electrocardiogram after relief of right ventricular hypertension. Phonocardiographic changes following surgery included marked changes in the stenotic systolic murmur and tendency toward normalization of the second sound, as evidenced by decrease in splitting interval between the aortic and pulmonary components, and either reappearance or increased amplitude of the second component. Development of a diastolic murmur of insufficiency occurred in 10 cases, all of which exhibited a good operative result. It is doubted that this murmur has any particular physiologic significance.

Radiographically a significant decrease in heart volume was obtained following surgery. Angiocardiographically good operative results were associated with either abolition of the valvular dome or by significant increase in ostium size.

Possible explanations of poor operative results are discussed.

The reported series showed no statistically significant difference in the results of the transventricular and transarterial valvulotomies. However, when an additional 99 patients from the literature were analyzed, there was a significant difference in the operative results of the 2 methods favoring the transarterial approach.

Acknowledgment

The authors are indebted to Dr. Gunnar Ekström of Crown Princess Lovisa's Hospital, Stockholm, for permission to include data of 5 of his patients. For catheterization data they also express their gratitude to the Cardiology Department, Crown Princess Lovisa's Hospital (patients 2, 14), and to Dr. Bernhard Landtman, Children's Hospital, Helsinki, Finland (patient 25).

Summario in Interlingua

Es presentate le resultatos clinic e physiologic obtenite in 25 patientes per chirurgia visante al alleviamento de stenosis pulmonar. Dece-sex patientes esseva operate per le methodo transventricular e 7 per le methodo transarterial. In plus, 2 infundibulectomias esseva effectuate.

Le mortalitate chirurgic esseva 7 pro cento pro omne le operationes. Le melioration clinic esseva uniformemente bon, sin reguardo al resultatos operatori.

Grados significative de melioration in deviationes anormal del axe electric e in hypertrophia dextero-ventricular esseva notate in le electrocardiogramma post alleviamento del hypertension dextero-ventricular. Le alterationes phonocardiographic post le intervention chirurgic includeva marcate alterationes del stenotic murmure systolic e un tendentia normalisatori in le secunde sono, evidentiate per un reducite intervallo de fisson inter le componentes aortic e pulmonar e re-apparition del secunde componente o augmento de su amplitude. Le disveloppamento de un diastolic murmure de insufficientia occurreva in 10 casos. In omne istos, le resultatos operatori esseva bon. Es opinate que iste murmure es sin special signification physiologic.

Ab le puncto de vista radiographic, grados significative de reduction del volumine cardiac esseva constatate post le chirurgia. Angioca-

diographicamente, bon resultatos operatori esseva associate con abolition del domo valvular e con un augmento significative del dimensiones del ostio.

Explicationes possibile de non-satisfactori resultatos chirurgic es discutite.

Le serie hic reportate non revelava un statisticamente significative differentia inter le resultatos obtenite per valvulotomia transventricular e illos obtenite per valvulotomia transarterial. Tamen, quando 99 casos additional ab le litteratura esseva analysate, un differentia significative appareva inter le resultatos obtenite per le 2 methodos. Le methodo transarterial se monstrava superior.

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This report summarizes the operative experience since 1945 of 36 prominent cardiovascular surgeons from several continents. Without surgical treatment, individuals with coaretation of the aorta have an average life expectancy of 32 years or less, and only 1 in 10 lives past the age of 50. Operation consists of resection of the coarcted segment; and the aortic defect may be bridged either with a homograft or with a woven plastic tube. Operative mortality rates in 1,601 patients averaged 8.6 per cent; and these deaths were attributed mainly to circulatory failure (33 patients) disruption of the anastomosis (28), ventricular arrest or fibrillation (18) or hemorrhage usually from dilated intercostal arteries (16). The postoperative results were satisfactory in 96 per cent of the 1,405 or more patients surviving operation by 3 months or longer. The blood pressure had returned to normal in 72 per cent and had been substantially reduced in an additional 23 per cent. Better results in the treatment of this relatively uncommon disorder are anticipated in the future from improvements in surgical technic and from the operations being done during childhood when operative mortality rates are lowest.

Rogers

Electrocardiographic Changes in Acute Subendocardial Infarction

I. Large Subendocardial and Large Nontransmural Infarcts

By Roderick W. Cook, M.D., Jesse E. Edwards, M.D., and Raymond D. Pruitt, M.D.

The electrocardiographic consequences of subendocardial infarction will find their most evident and characteristic expression in the acute phase of a large lesion. Five cases of this kind are presented here and the associated electrocardiographic changes are described. At what level in the myocardium between the endocardium and epicardium do the electrocardiographic expressions of subendocardial infarction give way to those of transmural infarction? Data in 6 cases of large nontransmural infarction are presented for comparison with findings in the 5 cases of subendocardial infarction.

Among the varied disorders that alter the form of the electrocardiogram, myocardial infarction is distinguished by the feature of localized loss of myocardial mass. When this destruction takes the form of a large transmural infarct, diagnostic alterations are commonly evoked in the QRS deflections of an electrocardiogram properly recorded by conventional technics. When the region of myocardial necrosis is confined to the inner layers of the left ventricular wall, changes in the QRS complexes of the scalar electrocardiogram may not be pathognomonic of this loss of myocardial substance. This fact is illustrated in the electrocardiographic and pathologic data reproduced in figure 1*a*. Destruction of a thick ring of myocardium lining the entirety of the left ventricular cavity in this case failed to produce a QRS configuration distinctive of myocardial infarction.

Among several excellent articles[1-3] on the electrocardiographic changes associated with subendocardial infarction, only in that of Myers and associates[2] were QRS changes reported of a character held to be significant and indicative of the subendocardial injury.

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Abridgment of portion of thesis submitted by Dr. Cook to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

In 1945, experimental studies[4] of the electrocardiographic consequences of subendocardial injury led to the conclusion that such lesions commonly are attended by loss in height of the R waves and the development of a small Q deflection or a notch low on the R wave in records taken from precordial leads overlying the traumatized wall of the left ventricle. In 1954, Prinzmetal and co-workers[5] reported loss of amplitude of the R deflection in 10 of 12 instances in which records were made from leads placed on the ventricular surface in a region overlying a subendocardial lesion produced by cautery.

When the clinical and the experimental data mentioned in the preceding paragraphs are combined, substantial support emerges for the view that those QRS alterations that attend subendocardial injury are of a kind subject to identification only in certain cases in which sequential records are available. Changes pathognomonic of localized loss of myocardial mass uncommonly present themselves in readily identifiable form in an isolated electrocardiogram.

If a clinical diagnosis of subendocardial infarction is to be supported electrocardiographically, experience on record would indicate that the major evidence will be derived from changes in portions of the ventricular complex other than the QRS deflection, namely the S-T segments and the T waves.

Experimental evidence supporting the concepts of the dipole theory with respect to the

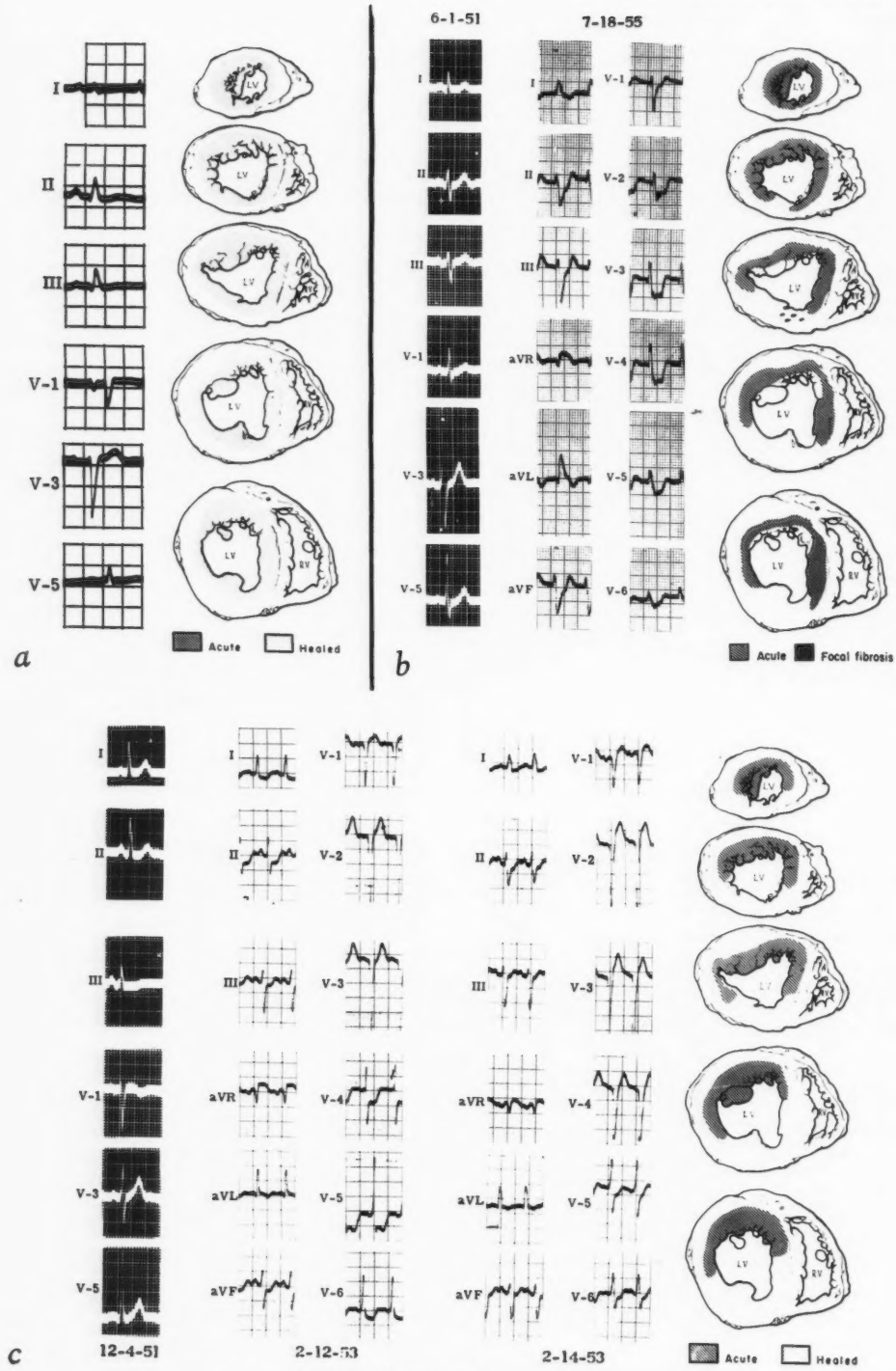

FIGURE 1. (*Legend on opposite page.*)

segmental shifts attending acute subendocardial injury was presented in 1948.[6] In 1955, evidence was reported suggestive of a relationship in certain instances between deeply inverted T waves in the precordial electrocardiogram and localized subendocardial injury.[7] The limited personal experience represented in these articles supports conclusions resting on a much larger body of evidence compiled in medical writing and summarized briefly as follows: 1. In acute subendocardial injury, as in other types of myocardial injury, segmental elevation will be recorded from a unipolar lead facing the most severely injured fibers, and segmental depression will be recorded from a lead facing the least severely injured fibers. Because of the nature of the leads commonly used in clinical electrocardiography, segmental depression as it occurs in the precordial electrocardiogram has come to be regarded as the usual expression of acute subendocardial injury or ischemia. However, segmental elevation in lead aV_R, which commonly reflects variations in potential like those encountered in a lead proximate to the great orifices at the base of the heart, is an equally consistent finding in subendocardial injury. 2. Deep inversion of T waves in precordial leads overlying the left ventricular surface may well be the expression of a transmural zone of ischemia, attended by actual necrosis of myocardial fibers in certain regions, most commonly the subendocardial .

Both segmental shifts and T wave inversions identical with those encountered in subendocardial infarction may occur in transient states of myocardial ischemia and may be resolved completely within a few minutes after the ischemic state has been relieved. This observation points up a fact of critical significance, namely that, unlike the QRS changes pathognomonic of loss of myocardial mass and hence of myocardial infarction, the segmental and T-wave changes associated with subendocardial lesions afford only inferential evidence of myocardial necrosis. Furthermore, since transient ischemia can produce changes of similar character, correlations between the degree of electrocardiographic alterations and the extent of morphologic changes must be of limited accuracy.

Methods and Materials

A review of the necropsy records at the Mayo Clinic from 1947 through 1955 disclosed 182 cases in which acute subendocardial infarcts were present. To simplify the correlation of electrocardiographic and morphologic changes, all cases were eliminated in which a healed as well as an acute infarct was present and in which available electrocardiographic data did not permit satisfactory distinction between the electrocardiographic consequences of the old infarct and the more recent lesion. Another and larger group of cases was eliminated in which any one of a variety of disorders existed that might have rendered difficult the proper identification of the origin of the electrocardiographic changes. Excluded on this basis were cases of pulmonary embolism, acute and chronic pericarditis, valvular heart disease, congenital heart disease, myocardial aneurysm, leukemic and granulomatous myocardial infiltration, pericardial effusion, severe ventricular dilatation, acute and subacute bacterial endocarditis, abscesses of the myocardium, cardiovascular syphilis, pronounced left ventricular hypertrophy, and digitalis intoxication. Of the original 182 cases, 152 were eliminated on the basis of one or the other of the preceding considerations.

The present report concerns 11 of the remaining 30 cases. These 11 cases are distinguished from the other 19 by the larger amount of acute myocardial necrosis present at necropsy. The 19 cases not included in the present account will form the basis of a portion of a second report.

Fig. 1. *a*. Old circumferential nontransmural infarction in a 36-year-old man. This patient had dyspnea on exertion for 2 years, and mild angina of effort for 1 year. He did not recall any symptoms of acute myocardial infarction. This electrocardiogram was made 4 days before death. *b* (Case 1). Acute circumferential subendocardial infarction in a 74-year-old man. Symptoms of infarction developed 10 hours before the electrocardiogram of July 18, 1955, was recorded. The patient died the next day. *c* (Case 2). Acute, nearly circumferential, subendocardial infarction in a 64-year-old woman who had acute granulomatous arteritis[8] attended by partial occlusion of coronary ostia. Anginal pain was first experienced 2 months before death. Pathologically, the infarct was judged to be 3 days old.

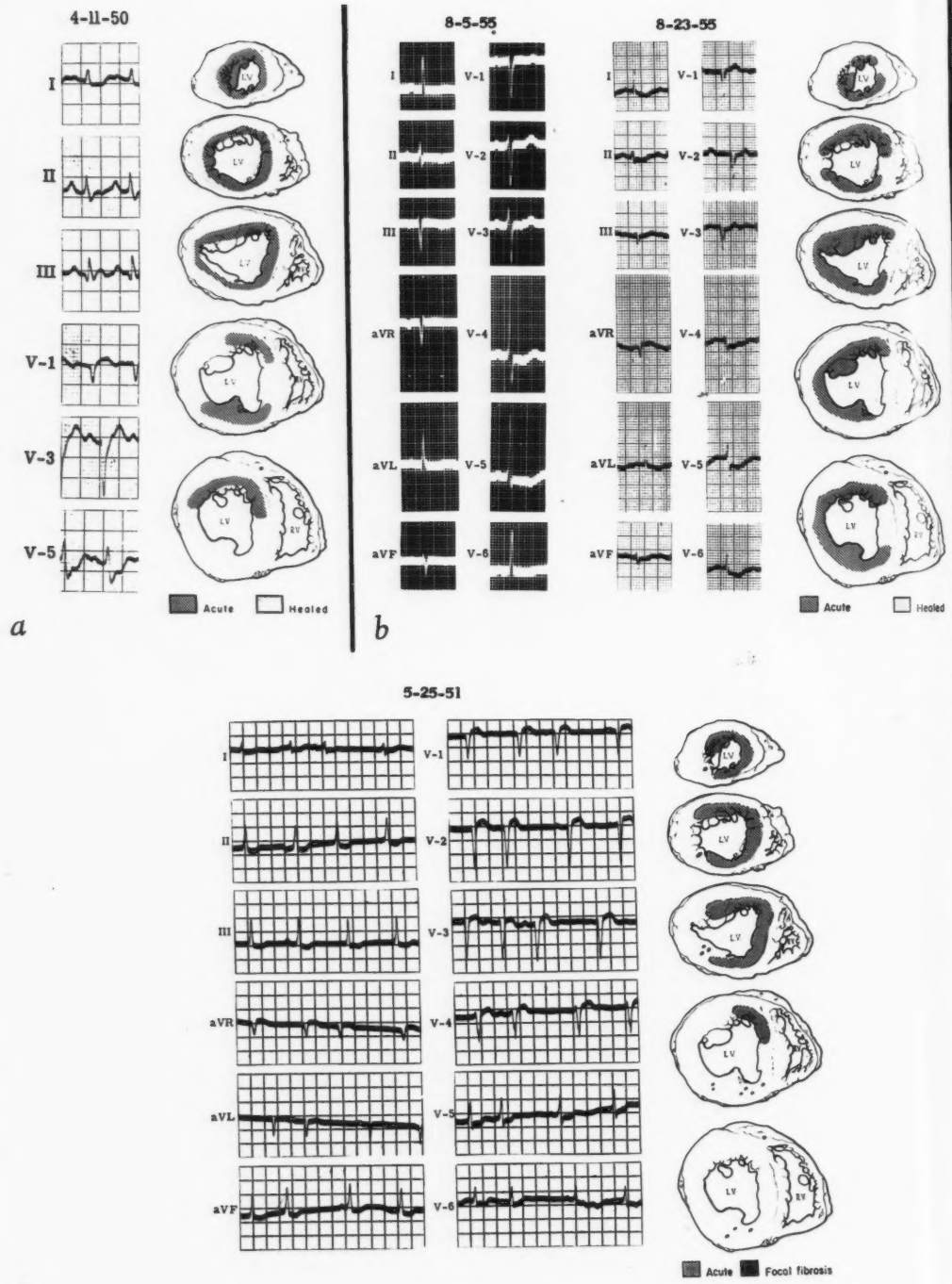

FIGURE 2. (*Legend on opposite page.*)

In all of the 11 cases in this study, the acute lesion involved at least 50 per cent of the circumference of the left ventricular wall and commonly achieved or approached circumferential extent in at least 1 of the 5 slices into which the heart was sectioned at right angles to its apicobasal axis.

In 5 of the 11 cases, the infarct throughout the major portion of its extent involved no more than the inner half of the total thickness of the ventricular wall. Lesions of this character will be referred to hereafter as "subendocardial," in distinction to the lesions in the remaining 6 cases, which will be called "nontransmural." In this latter group, some significant portion of the infarct involved more than 50 per cent but less than 75 per cent of the total thickness of the ventricular wall.

Results

Large Acute Subendocardial Infarcts. The 5 cases placed in this category form a group with satisfying homogeneity from both morphologic and electrocardiographic points of view.

Morphologically, a large subendocardial infarct was present involving always the anterior wall of the left ventricle together with circumferential or nearly circumferential invasion of the lateral or septal and, sometimes, the posterior portions of the left ventricular wall (fig. 1*b* and *c*, and 2). The oldest lesion in this group was in case 5 (fig. 2*c*) and was judged to be about 2½ weeks of age. In the other 4 cases, the infarcts ranged in age from approximately 10 hours to 3 or 4 days.

Electrocardiographically, a reasonably distinct pattern of changes could be defined as follows: 1. QRS deflections were characterized by low-amplitude R waves in V_{1-4}; in 3 instances in which preinfarction electrocardiograms were available (fig. 1*b* and *c*, and 2*b*), actual loss of amplitude occurred in R waves from these points, associated with the appearance of S waves in leads V_5 and V_6. 2. Q deflections were absent in all except case 1 (fig. 1*b*) in which such waves 1 mm. deep appeared only in leads V_2 and V_3. Complete loss of R waves was recorded in leads V_1 to V_4 in case 2 (fig. 1*c*). 3. Depression of the S-T segment in at least the left precordial leads was present in all instances, ranging from 2 mm. in case 5 to 7 mm. in case 1. Segmental elevation in lead aV_R was a consistent finding in those 4 cases in which this lead was recorded. 4. Although some peculiarities in QRS and segmental configuration occurred in standard limb leads and extremital leads other than aV_R, these changes were of lesser degree than they were in the precordial leads and varied in nature and distribution from case to case.

Clinically, the single feature common to all 5 cases was the critical nature of the patient's condition throughout the period subsequent to the postulated time of occurrence of the large infarct.

In case 1, a state of shock existed throughout the 10 hours from the onset of pain until the patient's death. In case 2, the patient's status was characterized by fever, tachycardia, pallor, dyspnea, orthopnea, and gallop rhythm. The existence of primary arteritis attended by occlusion of the major branches of the aortic arch precluded accurate appraisal of the blood pressure in the arms; in the legs, the pressure was 140 mm. Hg systolic and 90 diastolic. In case 3, the clinical picture was confusing from the diagnostic standpoint. After 3 days of severe abdominal pains attended by nausea and vomiting the patient was semicomatose and her blood pressure was 94/72. She died on the second day in the hospital. In case 4, the patient had severe angina pectoris for several months and had status anginosus 3 weeks prior to his death, which occurred abruptly and without preceding symptoms of shock. In case

FIG. 2. *a* (Case 3). Acute circumferential subendocardial infarction in a 57-year-old woman who had abdominal cramps, obstipation, nausea and vomiting for 3 days and who died on April 12, 1950. The acute infarct appeared to be 2 or 3 days old. *b* (Case 4). Nearly circumferential, acute subendocardial infarction in a 57-year-old man who had severe angina pectoris for 3 months prior to death, which occurred suddenly on August 23, 1955. The infarct was approximately 24 hours old. *c* (Case 5). Nearly circumferential, acute subendocardial infarction in a 71-year-old woman. Dyspnea and symptoms ascribed to "flu" had developed 3 weeks prior to death. She did not experience thoracic pain. On admission, she had severe congestive heart failure. She died within 24 hours, on May 25, 1951. The acute infarct was judged to be about 2½ weeks old.

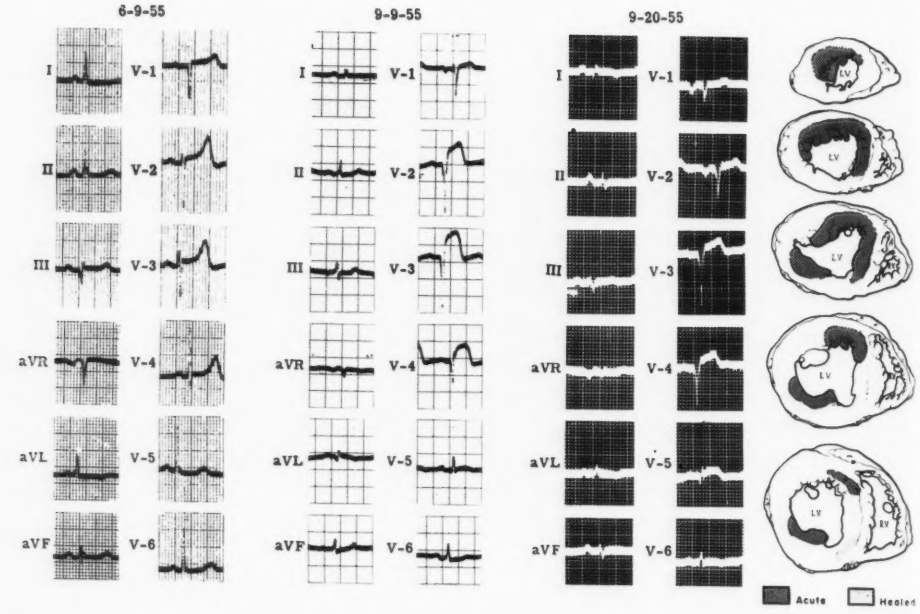

FIGURE 3. (*Legend on opposite page.*)

5, in which infarction occurred approximately 2½ weeks prior to death, the patient arrived at the hospital only a few hours before her death. She was in severe congestive heart failure attended by Cheyne-Stokes respiration. Her blood pressure was 118/80. The pulse rate was 120 beats per minute. She failed to respond to intensive treatment for congestive heart failure.

Large Acute Nontransmural Infarcts. The electrocardiographic behavior in this group of 6 cases can be developed appropriately by presentation of the findings in cases 6, 8, and 11.

In case 6 (fig. 3*a*), a 73-year-old woman had experienced episodes of anginal pain occurring at rest and lasting about 15 minutes at intervals of 1 to 2 hours for 3 days prior to her arrival at the hospital on September 9, 1955. She died abruptly and unexpectedly 15 days after admission. The acute infarct extended from one half to three quarters of the distance between the endocardial and epicardial aspects of the anterior wall of the left ventricle in the second and third slices from the apex (fig. 3*a*). The lesion was judged to be about 2 weeks old. Electrocardiographically, the infarct was attended by changes like those commonly encountered in an acute transmural anteroseptal myocardial infarct.

Case 7 resembled case 6 morphologically; electrocardiographically, the findings were only suggestive of acute anterior myocardial infarction.

In case 8 (fig. 3*b*), a 49-year-old man had experienced myocardial infarction 2 years earlier and died 14 hours after the onset of a second infarction. The acutely infarcted myocardium overlay the subendocardial scar and extended to the junction of the inner three fourths of the left ventricular wall with the outer fourth (fig. 3*b*). As in case 6, the electrocardiographic changes were those commonly associated with an acute transmural lesion; the findings were those of posterior infarction. Segmental depression in leads V_3 and V_4 was of unusually great degree.

Two other patients (cases 9 and 10) among the 6 who had large acute nontransmural infarcts had similar electrocardiographic findings.

In case 11 (fig. 3*c*), a 58-year-old woman had been subject to angina pectoris for 3 years prior to death, which occurred 2 days after the onset of symptoms of acute myocardial infarction. In the second slice from the cardiac apex (fig. 3*c*), the acute infarct extended over half the thickness of the left ventricular wall from the endocardium toward the epicardial surface. The electrocardiographic changes were nonspecific. The small Q waves in leads II, III, and aV_F probably were related to scarring of the posterior basal wall of the left ventricle. Segmental depression in leads I, II, aV_L, and V_6, and segmental elevation in aV_R and V_1 to V_4 probably were expressions of the acute infarct. The R waves in V_1 to V_4 were of low amplitude, and small Q deflections were present in V_5 and V_6.

Discussion

The electrocardiographic changes encountered in our 5 cases of large acute subendocardial infarcts conform to a pattern that might be derived from postulates based on the dipole theory and from clinical reports on the experience of others with cases in which similar types of lesion were present.[1, 3] The consistency with which these changes appear during the early hours of the development of such large acute lesions does not support the concept that the subendocardial region is electrocardiographically silent.[5] However, in contrast to the consistent appearance and impressive degree of segmental changes was the limited extent of the alteration in the QRS complexes. Here again, the nature of these changes was in conformity with experimental

FIG. 3. *a* (Case 6). Nearly circumferential, acute nontransmural myocardial infarction in a 73-year-old woman. On September 6, 1955, this patient experienced a pressure-like pain under the left breast, intensified on exertion. This pain subsided the next day but nausea and vomiting ensued. After some improvement death occurred abruptly on September 24, 1955. The infarct was judged to be approximately 2 weeks old. *b* (Case 8). Acute nontransmural infarction of the posterior wall of the left ventricle in a 49-year-old man. Symptoms of acute myocardial infarction began 14 hours prior to death, on March 31, 1955. *c* (Case 11). Acute nontransmural anteroseptal infarction in a 58-year-old woman. She had experienced a myocardial infarct 6 months prior to the final episode, which developed September 29, 1947. With this second attack she had congestive heart failure and increased anginal pain and she died on October 1, 1947. The acute infarct was judged to be about 2 days old.

evidence suggesting that loss of amplitude of R waves in precordial records is a more likely consequence of subendocardial injury than is the recording of large Q waves from these same leads.

The reasonable conformity between the electrocardiographic changes encountered in these 5 cases and those changes that would have been predicted on the basis of theory and experimental evidence should not lead to complacent acceptance of the view that all acute subendocardial lesions produce similar changes, nor that a large acute subendocardial infarct exists in all instances in which such changes are present. Exceptions to either of these conclusions will be presented in the forthcoming second portion of this report, which concerns small subendocardial infarcts.

The segmental deviations and QRS changes in 4 of the 6 cases of large acute nontransmural infarcts were of a kind commonly associated with transmural infarcts of comparable distribution. This group of cases is reported in an attempt to present facts bearing on 2 interesting questions: (1) at what level of the ventricular wall in a plane paralleling the epicardial and endocardial surfaces is destruction of myocardium attended by development of Q deflections in electrocardiograms derived from direct or semidirect leads; and (2) at what level of injury in the ventricular wall does the segmental depression of acute subendocardial injury as manifest in overlying epicardial leads give way to the segmental elevation in these same leads commonly associated with acute transmural injury. Since the definable morphologic boundaries of an infarct may not and probably do not coincide with the limits of injury (using the term "injury" in distinction to "ischemic" and "normally functioning" myocardium as regards electrocardiographic consequences), deductions derived from correlation of morphologic and electrocardiographic data must be viewed with appropriate circumspection. Such evidence as is presented here suggests that the level in question for both segmental deviations and QRS changes lies not less than half nor more than three quarters of the distance from the endocardium to the epicardium. Experimental evidence and theoretic considerations bearing on this problem have been presented in an earlier report.[7]

Summary

From a series of 182 cases in which acute subendocardial infarcts were present, 30 were selected for intensive study. The availability of appropriate electrocardiographic evidence and the absence of complicating lesions that might confuse the interpretation of such evidence were principal factors determining the selection.

The findings in 11 of these 30 selected cases are presented here. The remaining 19 will constitute a portion of another report.

Five cases included in the present account made up the category of large subendocardial infarcts of circumferential or nearly circumferential extent. Electrocardiographic findings in these 5 cases consistently conformed with that pattern postulated for acute subendocardial lesions on the basis of theoretic considerations, experimental evidence, and the clinical findings included in certain earlier accounts. Low-amplitude R waves were present in precordial leads V_1 to V_4; these waves were completely lost in 1 case. Preinfarction electrocardiograms were available in 3 of the 5 cases. Comparison of records before and after infarction revealed actual loss of amplitude in R waves from the 4 precordial points just noted, associated with the appearance of S waves in V_5 and V_6. Q deflections appeared in only 1 case; these deflections were 1 mm. deep and were present in leads V_2 and V_3. Depression of the S-T segment in at least the left precordial leads was present in all instances, ranging from 2 to 7 mm. Elevation of this segment in lead aV_R was also present in the 4 cases in which this lead was recorded. Although some peculiarities of QRS and segmental configuration occurred in standard limb leads and extremital leads other than aV_R, these changes were of lesser degree than in the precordial leads and varied in nature and in distribution from case to case.

In contrast to the electrocardiographic findings in these 5 cases of large acute subendocardial infarcts were those encountered in the 6 cases of large acute nontransmural infarcts. The changes in these cases generally were similar to those that would be anticipated as a consequence of acute transmural infarcts of similar distribution.

This evidence suggests that the change from a subendocardial to a transmural type of electrocardiographic pattern occurs when an infarct involves somewhat more than the inner half of the thickness of the ventricular wall.

Summario in Interlingua

Es un serie de 182 casos in que acute infarctos subendocardial esseva presente, 30 esseva seligite pro studios plus intense. Le disponibilitate del appropriate documentation electrocardiographic e le absentia de lesiones complicatori apte a confunder le documentation esseva le principal factores in determinar le selection.

Le constatationes in 11 del 30 seligite casos es presentate in iste reporto. Le remanente 19 casos va fornir le material pro un altere reporto.

Cinque del casos ineludite in le presente reporto constitueva le categoria de grande infarctos subendocardial dde dimensiones circumferential o quasi circumferential. Le constatationes electrocardiographic in iste 5 casos se conformava uniformemente con le postulationes pro acute lesiones subendocardial, facite super le base de considerationes theoric, de observationes experimental, e de constatationes clinic de publication anterior. Undas R a basse amplitude esseva presente in le derivationes precordial V_1 a V_4. Iste undas esseva completemente perdite in 1 del casos. In 3 del casos, electrocardiogrammas de un periodo pre-infarcimental esseva disponibile. Le comparation del registrationes facite ante e post le infarcimento revelava un perdita de amplitude in le undas R ab le 4 punctos precordial justo notate, associate con le apparition de undas S in V_5 e V_6. Deflexiones de Q appareva in solmente 1 caso. Iste deflexiones habeva un profunder de 1 mm e occurreva in V_2 e V_3. Depression del segmento S-T in al minus le derivationes precordial sinistre esseva presente in omne casos. Illo amontava a inter 2 e 7 mm. Elevation del segmento S-T in le deriation aV_D esseva etiam presente in le 4 casos in que iste derivation habeva essite obtenite. Ben que certe peculiaritates de QRS e del configuration segmental occurreva in le derivationes del extremitates altere que aV_D, illos esseva minus pronunciate que le alterationes in le derivationes precordial, e lor natura e lor distribution variava ab un caso al altere.

Le constatationes electrocardiographic in iste casos de grande acute infarctos subendocardial contrastava con le constatationes in le 6 casos de grande acute infarctos nontransmural. In istos, le alterationes esseva generalmente simile al alterationes expectate como consequentia de acute infarctos transmural de un simile distribution.

Iste observationes pare indicar que le transition ab le typo subendocardial al typo transmural in le configuration electrocardiographic occurre quando un infarcto comencia interessar plus que le medietate interior del spissitate del pariete ventricular.

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The anastomoses between coronary arteries present in the normal heart provide a basic collateral circulation, which while not sufficient to maintain myocardial contractions following acute interruption of the normal arterial supply, generally enable the survival of variable amounts of myocardium providing death does not follow the occlusion. In the survivors there is a gradual enlargement of collateral circulation quite variable in amount but sufficient to enable the ischemic myocardium to regain its contractile ability. The collateral blood comes exclusively from other arteries. The nearest artery or the anatomically shortest path of least resistance appears to be the commonest source and route.

Collateral coronary circulation was discussed from the standpoints of a historical review, physiologic studies of collateral coronary circulation, surgical approach to augmenting collateral coronary circulation, including abrasion of heart and pericardium, coronary sinus ligation, acute arterial retroperfusion of the coronary sinus, chronic arterilization of the coronary sinus, the mechanism of protection of arterial retroperfusion of the coronary sinus, implantation of internal mammary artery into myocardium, and metabolic factors operative in the augmentation of collateral coronary circulation. If and when it is possible to reduplicate the experiments of nature and completely interrupt all the normal inflow to the myocardium with survival, it should be possible to trace and measure the blood flow from the extracardiac arterial sources. Careful studies of treated and untreated groups with long-term follow-up are needed before precise answers can be reached. Much is yet to be learned, but the evidence at hand indicates that a firm foundation has been established for improving collateral circulation to the myocardium by surgical means.

Maxwell

Electrocardiographic Changes in Acute Subendocardial Infarction

II. Small Subendocardial Infarcts

By Roderick W. Cook, M.D., Jesse E. Edwards, M.D., and Raymond D. Pruitt, M.D.

Among 24 cases of small subendocardial infarctions included in this report are 10 cases of anteroseptal distribution in which the electrocardiogram was characterized by the presence of deeply inverted T waves in some or all of the precordial leads. Two other types of change encountered among the remaining 14 cases are described. Electrocardiographic changes in this group of 24 cases are compared with changes encountered in 5 cases of large and near circumferential acute subendocardial infarction described in part I of this study.

THE nature of the electrocardiographic changes attending 11 cases of large acute subendocardial infarcts from among a series of 30 cases of acute subendocardial infarction was reviewed in part I of this report. In part II, consideration will be given to the electrocardiographic changes encountered in the remaining 19 of the 30 cases that constituted this original series. Five additional cases will be considered. The latter cases failed to meet a criterion satisfied by all cases included in the initial series, namely, existence of an acute infarction at the time of necropsy. However, in each of these 5 additional cases, adequate electrocardiographic studies had been made during the presumedly acute phase of an infarction, the scar of which was delineated at the time of necropsy.

The 19 cases from the initial series combined with these 5 additional cases constitute a group of 24 cases in each of which a subendocardial infarct of small or moderate extent or scarring thereof was found at the time of necropsy. These 24 cases will be placed in 3 categories, allocation being determined by the position of the subendocardial infarct in relation to the circumference of the wall of the left ventricle. Ten cases from the initial series and the 5 additional cases fall in the category of anteroseptal lesions. Eight cases from the initial series fall in the category of posterior or posteroseptal lesions, and 1 falls in the category of lateral-wall lesions.

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I. Electrocardiographic Findings in Acute Anteroseptal Subendocardial Infarcts of Small or Moderate Size

Among the 15 cases in this category, 10 were characterized by the electrocardiographic finding of deeply inverted T waves in those precordial leads centered about position 3, 3 were characterized by the presence of segmental depression in the left precordial leads, and 2 by the existence of an intraventricular conduction disturbance suggestive of left bundle-branch block.

1. Cases Characterized by Deep Inversion of T Waves in Precordial Electrocardiogram. A. Cases Without QRS Changes Related to Anteroseptal Lesion. Seven cases were placed in this subdivision. The electrocardiographic and morphologic findings representative of this division of cases are illustrated in figure 1*a* and *b*. In the case represented in figure 1*a* an anteroseptal lesion was attended by deeply inverted T waves in precordial leads V_4 and V_5 and by shallow inversion of T waves in V_3, V_6, and standard leads I and II. In 3 other cases, findings of similar char-

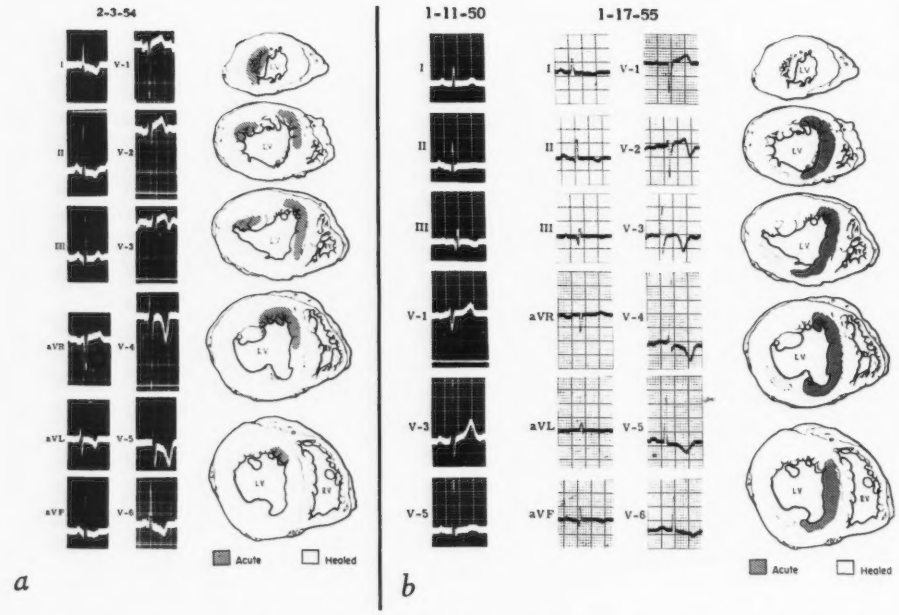

FIG. 1. *a*. A woman, 59 years of age, had angina pectoris 2 months prior to her death with an increase 15 days before death. She died abruptly on February 17, 1954. The electrocardiogram of February 3, 1954, was recorded on the day following increase in intensity of the patient's symptoms. This tracing is illustrative of the group characterized by deeply inverted T waves in the precordial electrocardiogram unattended by QRS changes. *b*. Acute subendocardial infarction in a man, 66 years of age, whose symptoms of infarction began 12 hours before the tracing of January 17, 1955 was recorded; death occurred 8 hours later. The origin of the Q deflection in leads II and III of the electrocardiogram of January 11, 1950 and in these same leads and in aV_F of the record of January 17, 1955 was ascribed to the scar in the posterolateral wall of the left ventricle. Deeply inverted T deflections in the precordial electrocardiogram appeared coincident with development of the acute septal subendocardial infarction.

acter were encountered. In the case illustrated in figure 1*b*, an acute anteroseptal lesion also was attended by similar T-wave changes. However, an old posterior scar was present and accounted for Q deflections in standard leads II and III. In 2 other cases, findings of similar character were encountered.

B. Cases Characterized by QRS Changes Related to Anteroseptal Lesion. Three cases were placed in this subdivision. The electrocardiographic and morphologic changes are illustrated in figure 2*a* and *b*. In figure 2*a*, an acute anteroseptal infarction was attended by deeply inverted T waves in precordial leads V_2 to V_5 and by lesser degrees of inversion in V_1 and V_6. R deflections in V_1 and V_2 disappeared transiently and the R in V_3 lost amplitude. In figure 2*b*, comparable changes in T deflections appeared at the time of the acute infarction; the R deflections in V_1 to V_5 decreased in amplitude and in addition small Q deflections appeared in V_2 and V_3. The findings in the third case in this group resembled those in figure 2*b*.

2. Cases Characterized by Segmental Depression in Left Precordial Leads. The electrocardiographic and morphologic findings in the 3 cases of this division are illustrated in figure 3*a*, *b*, and *c*. In figure 3*a*, segmental depression was present in leads I, V_5, and V_6, whereas segmental elevation of comparable

degree existed in leads V_2 and V_3. R waves were absent in V_1 and V_2 and a tiny R wave in V_3 was preceded by an equally tiny Q deflection. Posterior components of the lesion found expression in small Q deflections in leads II, III, and aV_F.

The findings in figure 3*b* included Q deflections in leads V_3 and V_5 in the record of October 24, 1949, related to old anteroseptal infarction. In the tracing of January 13, 1950, segmental depression related to the acute anterior subendocardial lesion was present in leads I, II, V_5, and V_6, whereas elevation of segments existed in aV_R. Twenty-four hours later, segmental shifts were of lesser degree but loss of amplitude in the R waves of leads V_1, V_2, and V_3 suggested additional destruction of myocardial substance in the anterior wall of the left ventricle.

The record of December 31, 1954, in figure 3*c* was made prior to development of the acute infarct of the antero-apical region. The old lateral-wall infarct probably resulted in loss of amplitude of R waves in V_5 and V_6 and in an increased R/S ratio in V_1. In the tracing of January 6, 1955, segmental deviations appeared indicative of severe subendocardial injury or ischemia. In leads I, II, aV_L, aV_F, and V_2 to V_6, this deviation was downward, whereas in aV_R, and to a lesser degree in V_1, it was upward.

3. Cases Characterized by Presence of Intraventricular Conduction Disturbance. The 2 cases in this division are represented by figure 3*d*. The electrocardiogram was taken a few hours prior to death in a patient found at necropsy to have an acute anteroseptal infarct approximately 1 day old. Scarring from a posterior infarct also was present. The electrocardiographic findings were a QRS interval measuring 0.12 second and a form of ventricular complex suggesting delay in excitation of the left ventricular surface. Segmental depression in leads V_5 and V_6 and elevation in aV_R were of a character similar to that seen in the other cases of acute subendocardial infarction of the anteroseptal region of the left ventricle presented in section I-2 of this discussion.

II. Electrocardiographic Findings in Acute Posterior or Posteroseptal Infarcts of Small to Moderate Size

In the 8 cases in which the major portion of the acute infarct was in the posterior or posteroseptal region of the wall of the left ventricle, the electrocardiographic findings were of varied character. Depression of the RS-T segments in left or in left and midprecordial leads was present in 5 of the 8 cases and represented the only suggestion of a type of change that might be held characteristic of these subendocardial infarcts of the posterior wall. In no instance did Q deflections which could be related to the acute subendocardial infarct develop in leads II, III, and aV_F. The range of variation in findings among these 5 cases is represented by the findings illustrated in figure 4*a*, *b*, and *c*.

In the case represented in figure 4*a*, the patient suffered from severe and frequently recurring bouts of anginal pain throughout the last 2 months of his life. His death occurred on October 26, 1954. Necropsy disclosed a small posterior infarct estimated to be 4 or 5 days old. The electrocardiogram of September 25, 1954 was made, therefore, approximately 3 weeks before the infarct developed, yet the segmental depression in the precordial leads is of only slightly lesser degree than in the record made on October 22, 1954 at a time when the acute infarct was present.

In the case from which findings are illustrated in figure 4b a moderately large posterior subendocardial infarct estimated to be 2 days old at the time of necropsy was associated with only slight segmental elevation in leads III and aV_F and with segmental depression in leads I, aV_L, and V_3 to V_6. The small Q waves in leads II and III had been present in the electrocardiogram of May 22, 1941 and probably were a product of the posteroseptal scars indicated in the diagrams of the cardiac slices.

In the case represented in figure 4*c*, a predominantly posterior subendocardial infarct became nearly circumferential in the 2 apically placed slices. Portions of this acute lesion appeared to be about 10 days old while

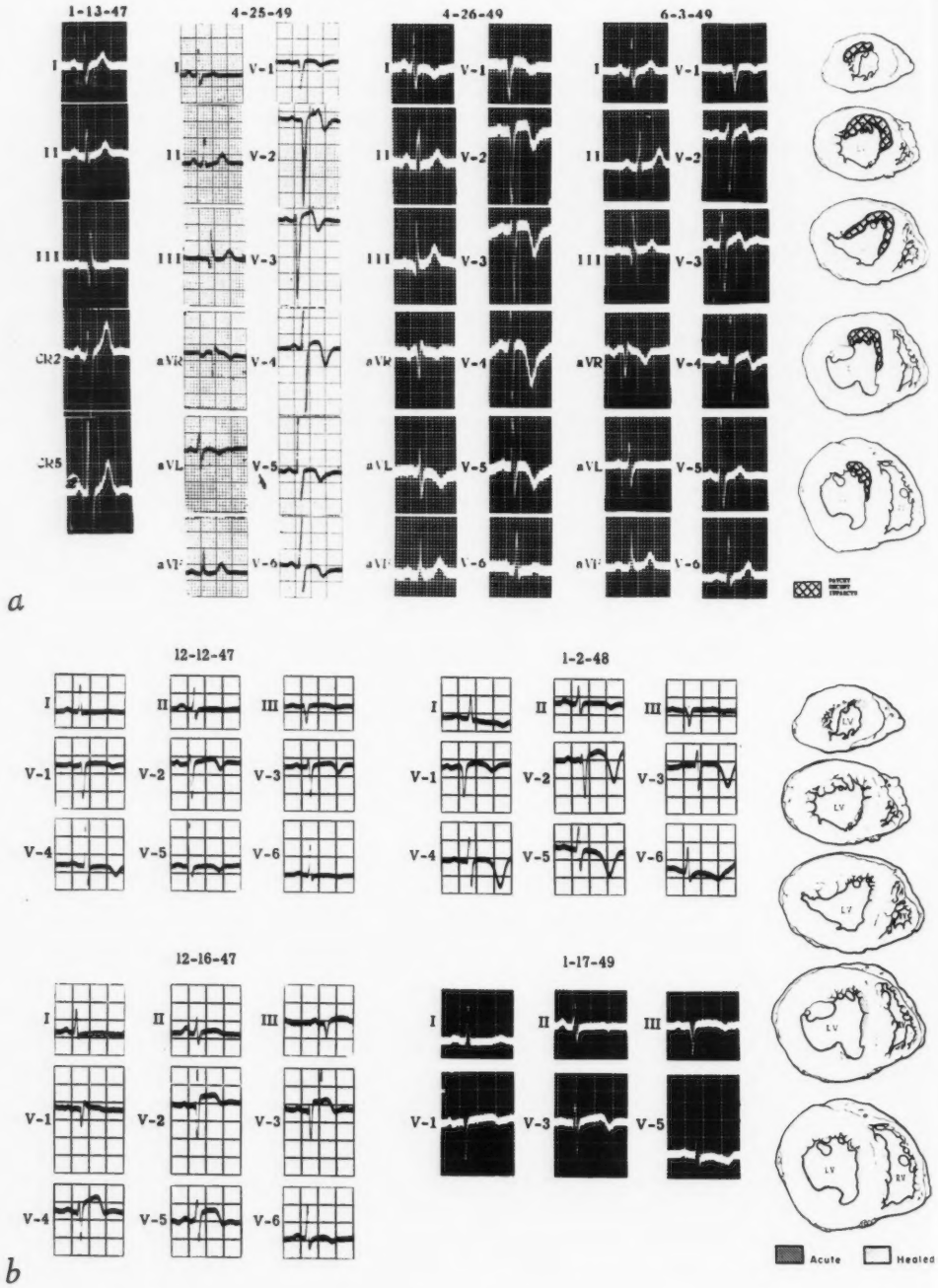

FIG. 2. *a.* Acute anteroseptal subendocardial infarction attended by transient decrease in voltage of R waves in precordial leads V_2 and V_3 and by deep inversion of T waves in precordial leads V_2 to V_5. The patient was a man, 47 years of age, who had an acute myo-

(*Continued on opposite page*)

a few areas were only a day or 2 old. The electrocardiogram of August 11, 1954 was made on the day of the patient's death. Apart from the segmental depression in V_6, only loss of voltage of deflections in the standard and extremital leads suggested myocardial changes in the electrocardiogram of a patient who had left bundle-branch block prior to development of the acute infarct.

Of the 3 remaining cases of the 8 with posterior or posteroseptal subendocardial infarcts, one (fig. 5*a*) was characterized by the development at the time of the infarct of right bundle-branch block and segmental depression in leads I and V_5 and by segmental elevation in lead III. In the other 2, represented by the findings in the case illustrated in figure 5*b*, small posterior infarcts produced no identifiable abnormalities in electrocardiograms recorded soon after onset of symptoms associated with development of the lesion.

III. Electrocardiographic Findings in Acute Subendocardial Infarction Involving Lateral Wall of Left Ventricle

The records in the 1 case in this category have been published elsewhere.[1]

Comment

To the 19 cases of acute subendocardial infarcts of small or moderate size originally included in this series were added 5 cases of anteroseptal subendocardial infarction. In all 5 of these added cases, electrocardiographic findings included deep inversion of T waves in the precordial electrocardiogram. Because of this fundamental uniformity among these added cases, observations regarding incidence of a certain type of electrocardiographic alteration must be made with appropriate allowance for the distorting influence of these added cases.

As regards acute anteroseptal subendocardial lesions, the conclusion appears justified that 2 types of change occurred most commonly but not in the same cases. These were deeply inverted T waves in the precordial electrocardiogram and depression of the S-T segments in all precordial or in left precordial leads, usually associated with elevation of segment in lead aV_R. QRS changes related to the acute infarction either were absent or were of limited extent. When present, these changes consisted of loss of amplitude in R waves in precordial leads V_1, V_2 and V_3 sometimes associated with appearance of small Q deflections in these same leads. Such changes occurred in 5 among 15 cases (3 cases under heading I-*1*-B and the first 2 cases under I-2). In 2 other cases (heading I-3) an intraventricular conduction disturbance suggestive of left bundle-branch block was present.

In no instance among the 8 cases of acute posterior or posteroseptal infarction were there Q waves related to the acute lesion. Only the finding of segmental depression in the left or left and midprecordial leads in 5 of the 8 cases could be held suggestive of a recurring pattern. Appearance of segmental depression in precordial leads in such cases is a finding discordant with simple predictions based on the dipole theory. Lesions of this distribution, if they influenced at all the segmental position in precordial leads, should produce elevation. The most likely basis for this discrepancy between theoretic prediction and recorded fact is lack of conformity between the boundaries of the infarct as defined at necropsy and the boundaries of the ischemic zone responsible for the segmental deviation. If the ischemic zone involved not only the myocardium immediately adjacent to the infarct but also extended into the apicolateral subendocardial regions, then segmental devi-

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cardial infarction on April 25, 1949. On June 3, 1949, within a few hours after the electrocardiogram was made, the patient experienced severe pain in his chest and died within a few minutes. The infarct outlined in the diagram was approximately 6 weeks old. *b*. Electrocardiograms recorded on a woman, aged 75 years at the time of her death in 1953. The tracing of December 12, 1947 was made when the patient was experiencing angina pectoris at rest. On December 13, 1947, she had a severe episode of pain lasting 3 hours. The electrocardiographic changes fall into the category of deeply inverted T waves in the precordial electrocardiogram associated with small Q deflection in leads V_2, V_3, and V_4.

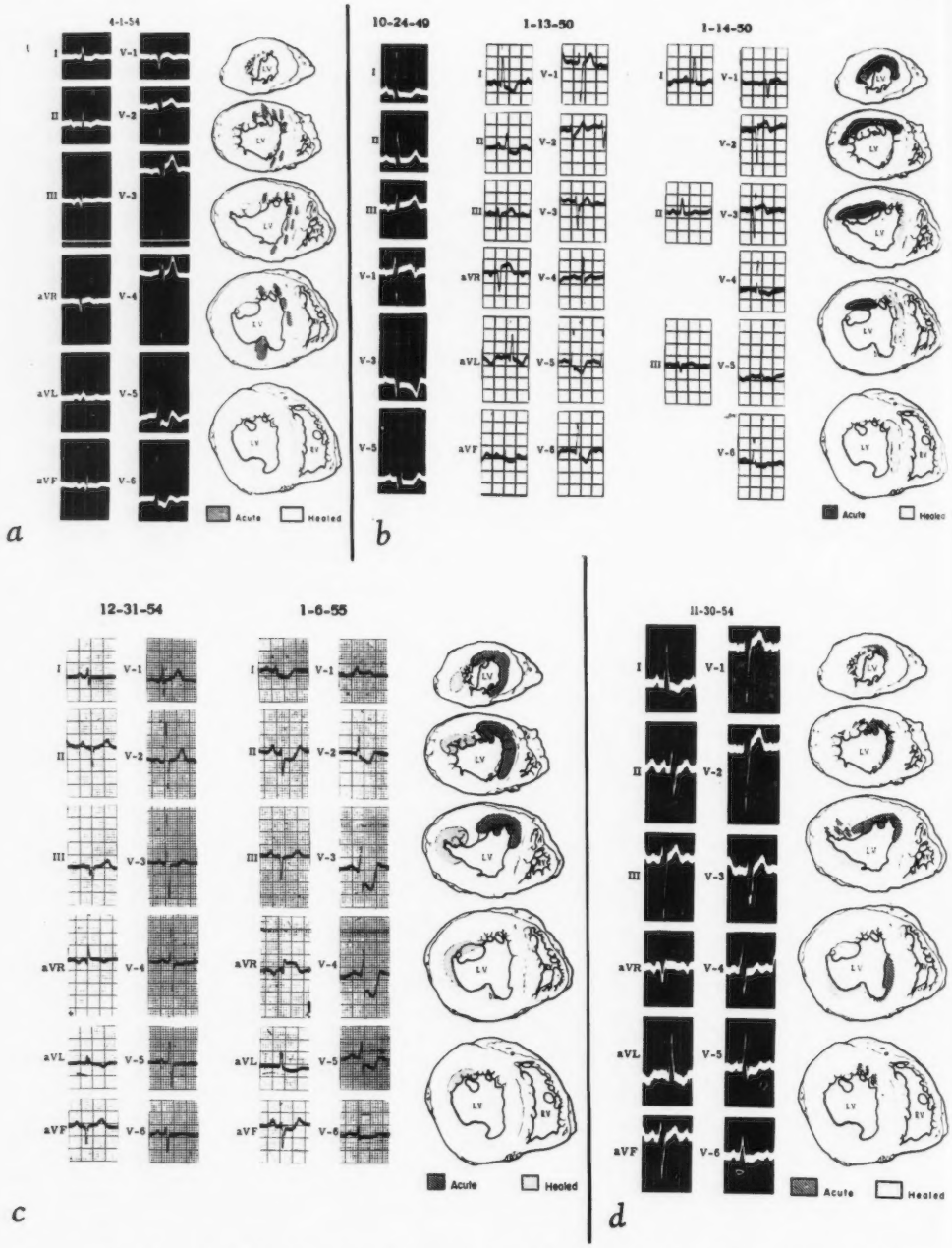

FIG. 3. *a.* Acute patchy anteroseptal subendocardial infarction attended by depression of RS-T segments in precordial leads V_5 and V_6 and by Q deflection in leads V_2 and V_3. The Q waves in leads II, III, and aV_F may be ascribed to the lesion in the posterior wall of the left ventricle. This lesion was older by approximately 1 week than the remainder. The patient, a man aged 82 years, died on April 7, 1954. Neither the clinical nor the pathological evidence rendered certain the presence of all portions of the patchy anteroseptal lesions when the

(*Continued on opposite page*)

ations of the kind recorded in the cases under discussion would be in keeping with predictions based on generally accepted theory.

A lack of conformity between the boundaries of the infarct and the boundaries of the ischemic zone reasonably should be anticipated. That such a lack of conformity occurs is substantiated by 2 other features of the data bearing on the correlation between infarcted myocardium and segmental deviations in the electrocardiogram. First, the correlation between size of infarct and extent of segmental deviations among the cases constituting this entire series is poor, even when allowance is made for possible failure to obtain an electrocardiogram at that time when segmental deviations were at their maximal extent. For example, an instance of striking segmental shifts in relation to a comparatively small infarct is found in the case represented in figure 3*c*. Second, in at least 1 case in this series (case represented in figure 4*a*), segmental deviations of similar distribution and degree were present in electrocardiograms made approximately 3 weeks before and on the day of occurrence of the infarct of the posterior wall of the left ventricle as found at the time of necropsy. While the infarct presumably developed in that portion of the myocardium where ischemia was most intense, and while existence of the zone of ischemic myocardium was responsible for the segmental changes, presence of infarcted tissue was only incidental to existence of segmental deviations.

In summary of these observations bearing on T-wave inversions and segmental shifts, it may be said that subendocardial infarction is the morphologic consequence of intense and sustained ischemia. In some instances the total region of ischemia may have been little larger than the infarct that developed. In other instances the infarcted myocardium may have represented only a small fraction of the total region of ischemia. Although segmental deviations and inversion of T waves were the principal electrocardiographic attendants of the acute subendocardial infarcts in this series, these electrocardiographic changes bear a specific relation to the ischemic and not to the infarcted tissue. The extent of infarcted tissue cannot be predicted from the degree of electrocardiographic changes encountered, and the very presence of infarcted myocardium is a deduction justified by, but not inherent in, the nature of the electrocardiographic changes.

When the electrocardiographic findings in the 5 cases of large and near-circumferential subendocardial infarcts presented in part I of this report are compared with the changes encountered in the present group of cases, certain differences are noted.

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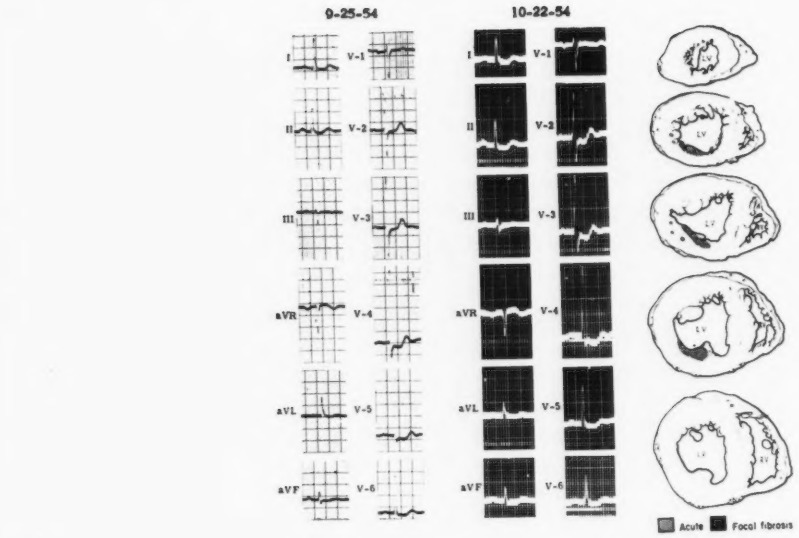
single electrocardiogram was recorded. *b*. Acute antero-apical subendocardial infarction associated with a healed anteroseptal lesion in a man, aged 56 years at the time of death. The electrocardiogram of October 24, 1949 was recorded approximately 12 hours after the patient experienced an attack of pain in the chest. The Q deflection in precordial lead V_3 was ascribed to effects of an anteroseptal infarct that presented as a scar at the time of necropsy. The tracing of January 13, 1950 was taken 5 hours after onset of a second episode. Significant features in this record included depression of RS-T segments in leads I, II, aV_F, V_5, and V_6, elevation of segment in aV_R, and loss of amplitude of R waves in V_2 and V_3. In the record of January 14, 1950 the R waves in V_2 and V_3 were even smaller. *c*. Acute anteroseptal subendocardial infarction in a man, aged 53 years, who had experienced an initial infarction 8 years previously. Episodes of severe chest pain occurred on December 29, 1954 and January 6, 1955. In the record of December 29, 1954 the tall R in V_1 and the small R in V_2 probably are expressions of the old infarct in the lateral wall of the left ventricle. In the record of January 6, 1955, major segmental deviations have appeared in relation to an episode of severe chest pain which began 6 hours before this tracing was made. Death occurred 12 hours later. The acute infarction was judged to be less than 24 hours old. *d*. Acute anteroseptal and old posterolateral infarction in a man, aged 48 years. Pain related to the acute lesion began on the day of the patient's death. At necropsy the acute infarct was judged to be about 12 hours old. The electrocardiogram shows changes indicating delay in excitation of the surface of the left ventricle. There was a Q deflection in aV_L. Segmental depression and upright T waves were present in leads V_5 and V_6.



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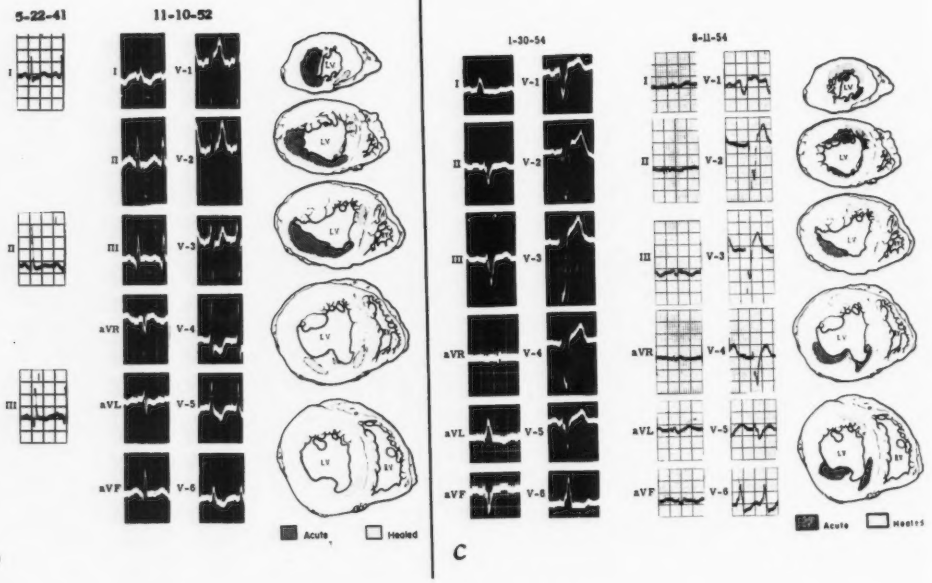

b *c*

FIG. 4. *a*. Acute subendocardial myocardial infarction in a man, aged 73 years, with severe angina pectoris and development of status anginosus in September 1954. On October 21, 1954, 5 days before death a particularly severe episode of pain occurred, probably with occurrence of a small subendocardial infarct of the posterior wall of the left ventricle. Note that segmental depression in leads I, II, and V_2 to V_6 and elevation of segment in aV_R were only slightly greater in the record made after development of the infarct than in the tracing made 3 weeks earlier. *b*. Acute posterolateral subendocardial infarction

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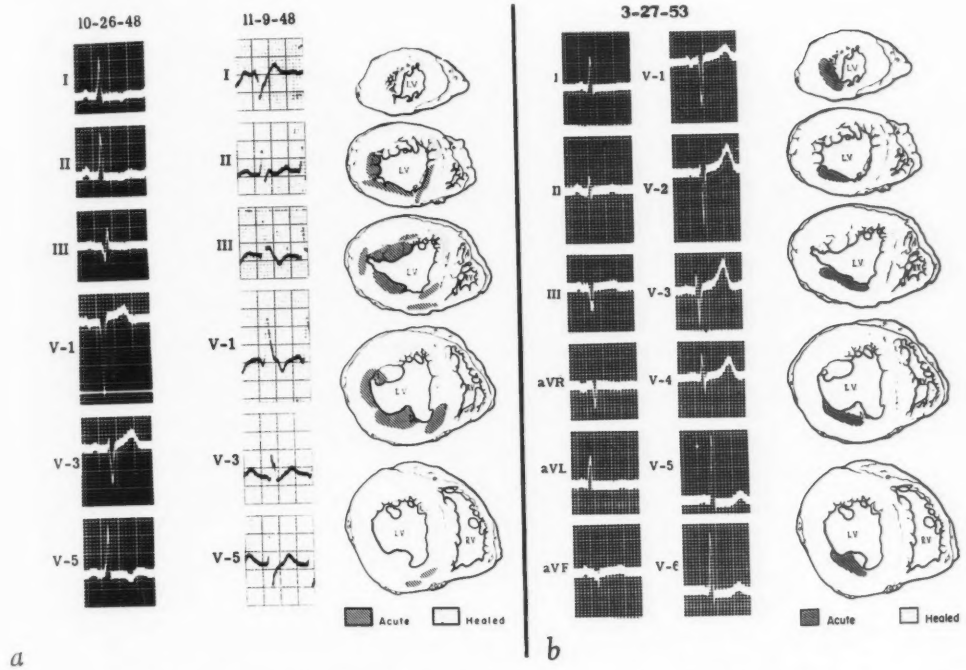

FIG. 5. *a.* Acute posterolateral subendocardial infarction associated with anteroseptal subendocardial scarring. The patient was a man, 64 years of age. The old infarction was judged to have occurred in 1947. Symptoms attending the acute infarction developed on November 9, 1948. The patient died the next day. In the record of November 9, 1948, evidence of right bundle-branch block was present. Segmental elevation existed in leads III and V_{-1} and segmental depression in leads I and V_5. *b.* Acute posterior subendocardial infarction in a man, 52 years of age. This patient had angina of effort for 1 year, nocturnal angina for 1 month, and intense and persistent pain for 2 days before his death on March 29, 1953. The electrocardiogram of March 27, 1953 was made within a few hours after onset of intense pain. The pathologic findings were compatible with an infarct of 2 days' duration. Electrocardiographic evidences of the infarct are minimal. The QRS complex in aV_F is polyphasic and of low voltage. T deflections in leads I and aV_L are flat. RS-T segments in V_5 and V_6 are depressed 1 mm.

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associated with healed lesions of posterior and septal location. The patient was a man, 58 years of age. The tracing of November 10, 1952 was recorded 1 day after the onset of symptoms of myocardial infarction and 1 day prior to the patient's death. Q waves were present in the tracing dated May 22, 1941 and these persisted unchanged in the record of November 10, 1952. Segmental depression and inversion of T waves were present in leads I, V_4, V_5 and V_6 of the latter record. The RS-T segment in aV_R and V_1 was elevated. *c.* Acute postero-apical subendocardial infarction associated with anterior subendocardial scarring in the presence of left bundle-branch block. The patient was a woman, 60 years of age. Symptoms of myocardial infarction developed on August 10, 1954 and the patient died the next day. The changes in the electrocardiogram between January 30, 1954 and August 11, 1954 probably are a consequence of the acute lesion, since the old infarct was believed to have occurred in July 1953. Note loss of amplitude of QRS complexes in standard limb and extremital leads and greater segmental depression in lead V_6.

1. Whereas the pattern of deeply inverted T waves in the midprecordial lead was not encountered in the group of large, near-circumferential infarcts, it appeared in 5 of the cases originally included among the small acute subendocardial infarcts and in 5 additional cases appended to the series.

2. Segmental depression in precordial leads and segmental elevation in lead aV_R were common attendants both of acute anteroseptal and of acute posterior or posteroseptal infarcts of small or moderate size. However, the incidence of this change approximated 50 per cent in the 19 cases in the original series of this type of infarct, whereas segmental depression occurred in all cases of large acute subendocardial infarction. Furthermore, the degree of depression commonly was greater in the presence of the larger infarcts.

3. When QRS changes did attend development of small anteroseptal subendocardial infarcts, the nature of these changes was similar to the nature of those occurring with large subendocardial lesions. However, the incidence of such changes was less in association with the small lesions (3 among 8 cases; in 2 additional cases there were intraventricular conduction disturbances) than with the large lesions (all 5 cases). Q waves related to the acute infarction did not appear in lead II, III, or aV_F in the group of 8 posterior or posteroseptal lesions.

Summary

1. The electrocardiographic findings have been presented in 19 cases of acute subendocardial infarcts of small or moderate size, and in 5 additional cases of anteroseptal infarcts in which electrocardiograms were recorded at a time when other clinical data indicated the lesion was acute.

2. Three types of electrocardiographic change related to the acute phase of the infarction were encountered most commonly. These were: (a) depression of the RS-T segments in all precordial or in the left precordial leads, (b) deeply inverted T waves in some or all of the precordial leads, and (c) diminished height of R waves sometimes associated with appearance of small Q waves in certain precordial leads.

3. Because QRS changes are of so limited an extent and RS-T-segment and T-wave changes afford no specific indication of myocardial infarction as contrasted with subnecrotic myocardial injury or myocardial ischemia, the electrocardiographic delineation of subendocardial infarction is commonly inferential as to the fact of occurrence and nebulous as regards extent and configuration of the lesion.

Summario in Interlingua

1. Es presentate le constatationes electrocardiographic in 19 casos de acute infarctos subendocardial de micre o moderate dimensiones e, in plus, in 5 casos de infarctos anteroseptal in que le electrocardiogrammas esseva obtenite a un tempore quando altere datos clinic indicavo que le lesion esseva acute.

2. Esseva incontrate le plus communmente 3 typos de alterationes electrocardiographic in association con le phase acute de infarcimento. Illos esseva (a) depression del segmentos RS-T in omne derivationes precordial o al minus in le derivationes sinistro-precordial, (b) profundemente invertite undas T in omne le derivationes precordial o in alicunes de illos, e (c) reducite altor del undas R, a vices associate con le apparition de micre undas Q, in certe derivationes precordial.

3. Proque le alterationes de QRS es si restringite in lor dimensiones e proque le alterationes del segmento RS-T e del unda T non permitte le differentiation inter infarcto myocardial e subnecrotic compromisso myocardial o ischemia myocardial, le delineation electrocardiographic de infarcimento subendocardial es generalmente inconclusive quanto al facto del presentia del lesion e vage quanto al extension e al configuration de illo.

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Quantitation of Valvular Regurgitation from Multiple Indicator-Dilution Curves

By RAMON L. LANGE, M.D., AND HANS H. HECHT, M.D.

Dye-dilution curves obtained simultaneously from the pulmonary artery and from the femoral artery following an intravenous injection of T 1824 or Indocyanine Green in normal subjects and in patients with nonregurgitant heart disease yielded a similar contour. This suggested that in the absence of regurgitation the parameters of the distal (arterial) curve can be predicted from the proximal (pulmonary artery) curve. The distortion of the arterial curve by regurgitation can therefore be compared with the undistorted pulmonary artery curve. To the extent that 2 identifiable and measurable flow rates exist between the sites of sampling, a theoretical basis for quantitation of the degree of valvular regurgitation may be derived.

SEVERE instances of pure stenosis and pure regurgitation can usually be recognized with little equivocation by clinical methods. However, the diagnosis of "predominance" of one type of valvular deformity over the other is of considerable practical importance when surgical intervention is contemplated, since clinical findings may be misleading. Some examples of pure stenosis may even appear with signs commonly associated with regurgitation.[1] The combined use of right heart, left heart and aortic catheterization has permitted a precise analysis of pure obstructive valvular disease,[2-5] but equally satisfactory methods for the estimation of valvular regurgitation are not as yet available.

Few quantitative attempts to estimate aortic incompetence in man have been made. The procedure of Braunwald and co-workers[6] and that of Warner and Toronto,[7] are the only recent attempts to assess aortic regurgitation. For mitral insufficiency, several approaches have been tried: 1. Attempts have been made to correlate the size of the left atrial (LA) or pulmonary wedge (PA-W) pressure pulses with the degree of regurgitation,[8, 9] and the detailed aspects of one or the other of the recorded parameters of the contour of the pressure curve have been used. In some instances vasoconstrictor drugs, which are said to unmask or to accentuate apparent diagnostic changes in pulse form, have been used in addition.[10] Data obtained in this way, however, have in general been unreliable because information concerning (a) the forward nonregurgitated flow and (b) the volume of the receptacle into which regurgitation occurs has not been available.

2. On the other hand, shunting of blood away from the forward path in examples of congenital heart disease has been quantitated by the use of indicator substances whose path could be traced within the central circulation.[11-13] Empirical analysis of such curves has allowed a certain quantitation of left-to-right shunts that agrees with estimations made from blood gas analyses and oxygen consumption. If congenital "regurgitation" of atrial, ventricular or great vessel defects is qualitatively similar to acquired regurgitation, the same general concept should apply in an analysis of the latter. Attempts have been made in the case of mitral regurgitation to obtain quantitation by injecting an indicator substance into the left ventricle through a transthoracic puncture, left atrial blood being sampled simultaneously.[5, 14-16] It was thought that the retrograde appearance of any indicator, before recirculation, should be proportional to the amount of blood regurgitated. This method is sensitive to the catheter position within the ventricle, and therefore the as-

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TABLE 1.—*Normal or Nonregurgitant Heart Disease*

Patient	Name	Age	Sex	Diagnosis	Degree of heart failure	Chamber enlargement	ΔMCT (sec.)	ΔAT (sec.)	ΔT (sec.)	Q_F L./min.
1	F.G.	23	M	N	0	0	4.7	4.0	.7	5.7
2	L.H.	21	M	N	0	0	6.8	6.5	.3	6.9
3	M.T.	26	M	N	0	0	7.6	7.0	.6	10.8
4	L.C.	25	M	N	0	0	3.5	3.5	0	7.6
5	C.B.	21	M	N	0	0	10.5	9.7	.8	7.3
6	F.C.	19	M	N	0	0	10.3	9.0	1.3	4.0
7	C.Y.	22	M	N	0	0	9.4	8.5	.9	5.6
8	J.D.	20	M	N	0	0	10.9	9.2	1.7	6.8
9	F.W.*	27	M	anemia	0	0	9.0	9.0	0	12.0
10	A.K.	57	M	cor pulmonale	4+	RV and LV	13.7	13.0	.7	7.1
11	W.K.	47	M	cor pulmonale	4+	RV and LV	11.0	10.0	1.0	4.8
12	B.C.	29	F	MS	0	LA, 2+	5.5	5.5	0	5.5
13	W.D.	34	M	AS	0	LA, LV 1+	7.0	7.0	0	8.0
14	D.C.	25	M	AS	0	LA, LV 2+	11.0	10.0	1.0	5.6
15	T.J.	30	M	MS	1+	LA, 2+	12.0	11.0	1.0	4.7

*Dye injection into right atrium.
MS, mitral stenosis
AS, aortic stenosis
N, normal heart
LA, left atrial
LV, left ventricular
RV, right ventricular
$\Delta T = 0.6$
($\delta x = 0.55$
$\delta m = 0.15$)

sumption of complete mixing within the ventricular as well as the atrial chambers that underlies this approach is not always correct. Though quantitation appears possible at times, these methods may be misleading, particularly when they indicate little or no regurgitation.

3. An approach which may not suffer from the problems of mixing is that of Korner and Shillingford, who have analyzed the disappearance slope or the variance of the earpiece oximeter curve following a single injection of dye into a peripheral vein (or right heart).[17, 18] They have compared such curves with values obtained from a set of given standards. The formula obtained from normal subjects by which regurgitation is estimated may not always apply, since variables such as the effective volume of the central circulation remain unknown. The method offers simplicity and elegance of theory, but gives no direct information concerning the effects of regurgitation alone, which are separate from those of alteration in flow and volume. One should know, in any given subject, what the configuration of the dilution curve would have been if no valvular regurgitation had been present. A somewhat similar approach has been described by Keys, Swan and Wood.[19]

If one were to obtain in 1 individual 2 dilution curves simultaneously, 1 from a nonregurgitant and 1 from a regurgitant portion of the system, it might be hoped that the former curve could be used to predict the form of the latter if no regurgitation were present. The difference between the observed curve and the predicted curve in the regurgitant system would be a function of the regurgitation. We have attempted this approach and in the following describe the right and left heart circulation in normal subjects, in patients with (a) nonregurgitant heart disease, and (b) with aortic regurgitation, mitral regurgitation and a combination of both.

METHOD

Human Subjects

The experiments were carried out on 9 normal subjects, 6 patients with heart disease and 1

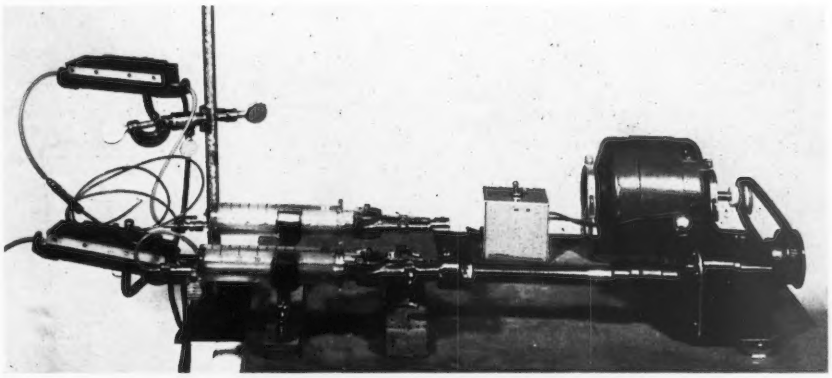


FIG. 1. Syringe puller designed for constant, equal and reproducible sampling of blood through cuvet oximeters. Variable gear ratios allow close adjustment of screw rotation that controls movement of syringe plungers.

regurgitation, and 31 patients with valvular regurgitation (tables 1 and 2). The observations were made with the patient in a steady resting state, and net forward cardiac output (Q_F) was determined by the Fick principle with use of oxygen consumption and oxygen arteriovenous difference, and by dye-dilution curves in the usual manner,[20] but with direct recording cuvet oximeters.[21] Pressures were recorded by means of an optimally damped catheter strain gage system. A catheter remained in the pulmonary artery (PA) throughout the test period. Three to 5 ml. of a 1 per cent solution of T 1824* were injected and "flushed" into a peripheral vein (occasionally into the superior vena cava or right atrium) during a period not exceeding 1 second. Simultaneous sampling from the catheter and from a needle in a femoral artery was accomplished by means of a device that moved the plungers of matched 50-ml. syringes in tandem by a constant-speed motor-driven worm-gear drive at 0.5 to 1.0 ml. per second (fig. 1). The blood was drawn through equisensitive direct-recording Wood oximeters. The procedure was generally duplicated and bracketed between Fick output determinations. The catheter transit time for blood was measured separately.

In the carrying out of these procedures several additional points had to be considered. 1. The presence of reduced hemoglobin in the PA sample could distort a dye-dilution curve when compared with the fully oxygenated arterial sample. When tracings with uneven baselines were rejected this was found to be not a significant factor. Several PA samples obtained with Indocyanine Green ("Cardio-Green"),* a substance with infrared absorption, independent of hemoglobin concentration, yielded identical data. 2. "Smearing" of the PA dye curves sampled through a long catheter, as compared to a femoral sample obtained by needle puncture, was found to be negligible when sampling was accomplished through the syringe puller. This was tested in several experiments on dogs with the equipment described above. No difference could be seen in dye-dilution curves sampled in this manner through catheter or needle (fig. 2). 3. Skewing of dye curves due to the distorting effects of the peripheral arterial vascular bed[22] was avoided by sampling from the femoral artery exclusively and disturbing flow as little as possible.

Courtesy of Warner-Chilcott Laboratories.

Model Experiments

The observations on human subjects were complemented by models in an attempt to construct a simple system yielding similar dye curves. The model consisted of 2 "ventricles" with a matched pulsatile flow provided by a Sigma finger pump. The dye mixture was injected proximally to the right ventricle and arrived well mixed. Simultaneous sampling from the right and from the left ventricular outflow was accomplished by using the same oximeter sampling device discussed above. Single or multiple connections between the 2 chambers constituted "the lung." Left ventricular "regurgitation" was produced by increasing the left ventricular stroke volume and allowing the excess volume to recirculate (fig. 7). For reasons to be discussed, the proximal sample was taken as close as possible to the regurgitant system.

*Courtesy of Hynson, Westcott, & Dunning.

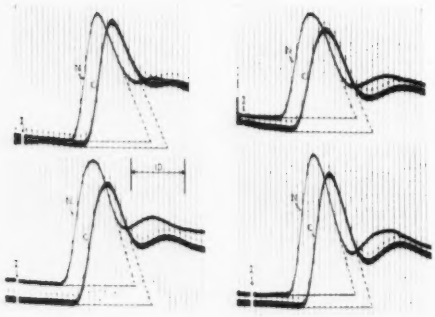


FIG. 2. A series of single arterial dilution curves sampled by needle (*N*) and catheter (*C*) from same site. Rate of sampling is of order usually used. Note absence of effect on C curve due to catheter passage.

RESULTS

Observations on Normal Subjects, on Patients with Nonregurgitant Heart Disease, and on Models.

With use of the technic described above, an interesting similarity involving all parameters of the curves could be demonstrated in all 9 normal subjects and in 6 patients with heart disease but without regurgitation. The similarity was observed to be independent of chamber size, cardiac output, or the presence of congestive failure (table 1, fig. 3). The well-known difference in the appearance of a congestive failure curve with that of a normal dye-dilution curve[23] was, of course, recognized, but this was present to an equal degree in the PA sampled and femoral artery (FA) sampled curves (fig. 3).

When in the model an attempt was made to simulate conditions that would yield a set of nearly identical curves, it was noted that only a direct connection, consisting of a single tube between right and left ventricle, would reproduce such curves. The model and data from a single tube "lung" experiment are reproduced in figures 4 and 5.

The observations of human subjects without regurgitation, and of the nonregurgitant model demonstrating near identity of the curves, strongly suggest that all pathways between the 2 sampling sites are traversed with essentially equal speed. Thus the time it takes for any given particle of dye to travel from one site to the other would be similar and the points on the 2 curves that define this particle would occupy the same relative position on each curve.

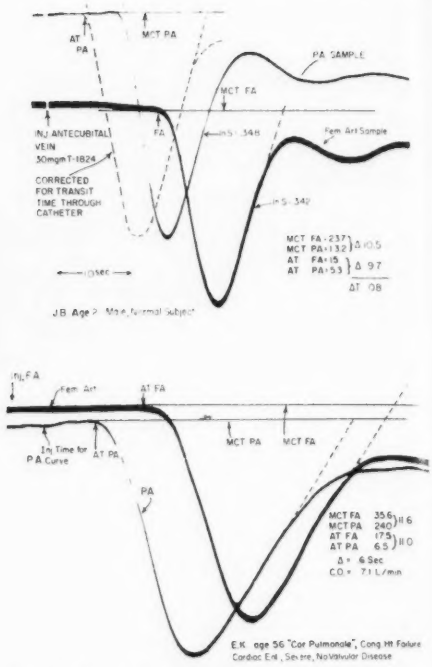
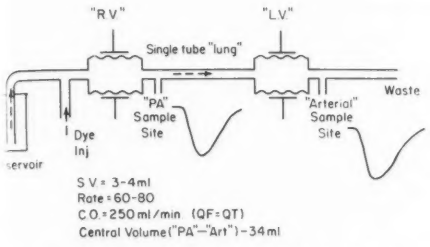


FIG. 3 *Top.* Unretouched dye-dilution curves in young normal resting adult male (subject no 5 of table 1), sampled from pulmonary artery (*PA*) and femoral artery (*FA*). Note similarity in all parameters of 2 curves. Sampling rates cause delay in inscription of *PA curve* of 4 seconds due to volume of catheter sampling system. "True" *PA curve* corrected for delay in catheter system is indicated by *dashed line*. In subsequent figures curves are corrected by adjustment of the "injection time" forward by an interval equal to the catheter delay. The disappearance slopes (lnS) of the 2 curves are nearly identical. *Bottom.* Curves obtained as in *A* from 56-year-old man in heart failure due both to emphysema heart disease and to arteriosclerotic heart disease with generalized chamber enlargement (patient 10, table 1). Despite longer passage time of both curves, delay of disappearance of slopes, and absence of a discrete recirculation deflection, relationships are similar to normal subject (*A*) and both curves are nearly identical.



IG. 4. Diagram of a hydraulic model of 2 "ventricles" in series. The lung is a single tube. Curves from "PA" and "arterial" sites are traced. *S.V.*, stroke volume; *C.O.*, output; Q_F, forward flow; Q_T, total flow.

Selecting arbitrarily (a) the *shortest* observed transit time of dye particles, characterized by the beginning of the inflection of the 2 curves and designating these "appearance times" as AT_{PA} and AT_{FA} respectively, and (b) designating the *average* particle circulation time that elapses between all points as "mean circulation time" MCT_{PA} and MCT_{FA} respectively, we find that in the normal subjects and in patients without regurgitation the 2 sets of measurements are nearly identical. In consequence, the differences in the 2 appearance times $AT_{FA}-AT_{PA}$ (henceforth to be called ΔAT), and the differences in the 2 mean circulation times $MCT_{FA} - MCT_{PA}$ (henceforth to be called ΔMCT) are similar. The small systematic difference between these (called $\overline{\Delta T}$) averaged 0.6 second (table 1.). This small difference could not be correlated with any known parameter, and must be considered a characteristic of the nonregurgitant system under these circumstances. It is applied as a correction factor, as seen in table 2.

Observations on Subjects with Regurgitation and on the Insufficiency Model

Figure 6 illustrates examples of valvular regurgitation of varying severity. The difference between the 2 simultaneously recorded curves is at once apparent and contrasts with the extreme similarity of all parameters of the 2 curves in the nonregurgitant system of figures 3 and 5. As seen alone, the distal

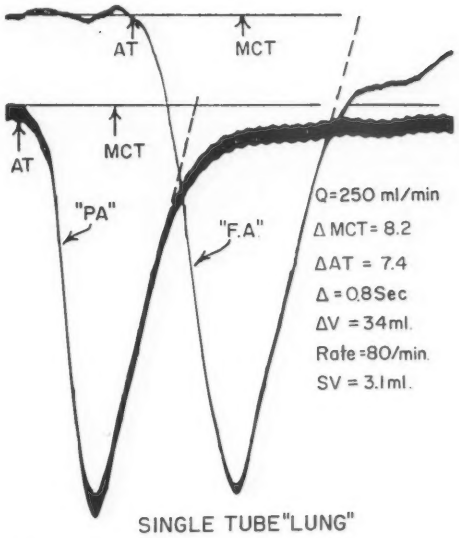


FIG. 5. Dye-dilution curves obtained from model of figure 4 with injection at site indicated in figure 4. Note essential similarity of PA and FA curves, which reproduces a set of tracings such as illustrated in figure 3.

curves of figure 6 might be considered normal in the first case (*top*) but not in the second case (*bottom*). However, the distal curve in the second case, of figure 6, might be confused with that observed in severe heart failure, which it closely resembles. In both instances the distal curves can be interpreted only in the light of their deviation from the proximal curve. Table 2 summarizes the data on cases of valvular regurgitation analyzed in this manner.

The changes in the relation of the 2 simultaneously inscribed dye-dilution curves were always of a similar kind: while ΔAT, the difference between the 2 appearance times, was of the same order of magnitude seen in the normal controls, the changes in ΔMCT, the differences in the respective mean circulation times, were larger. This essentially describes a change in the variance and in the disappearance slope of the dye curve obtained from the regurgitant system. Observed alone and of itself, it has no apparent advantages over direct slope measurements, or the reciprocal

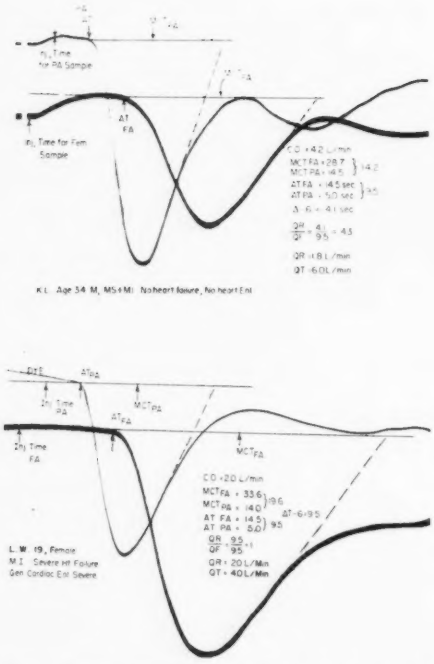

Fh Time for PA Sample
Fh Time for Fem Sample
CO = 4.2 L/min
MCTFA = 28.7
MCTPA = 14.5
ATFA = 14.5 sec
ATPA = 5.0 sec
ΔT = 9.1 sec
QR/QF = 4.1/9.5 = 4.5
QR = 4.8 L/min
QT = 6.0 L/min
K.L. Age 34 M, MS+MI. No heart failure, No heart Enl.
Fh Time PA
Fh Time FA
CO = 20 L/min
MCTFA = 33.6
MCTPA = 14.0
AT FA = 14.5
AT PA = 5.0
ΔT = 9.5
QR/QF = 9.5/1
QR = 20 L/Min
QT = 40 L/Min
L.W. 19, Female
M.I. Severe Ht Failure
Gen Cardiac Enl Severe

FIG. 6 *Top.* Dye-dilution curves in mitral regurgitation. Curves from patient 7, table 2. Arterial curve (FA), if seen alone, would pass as normal with usual contour and even a discrete deflection of recirculation. Viewed in comparison with the PA curve, however, it is markedly altered from normal. The patient was explored surgically and a moderate degree of valvular regurgitation was found, correlating roughly with estimates of 40 per cent regurgitant flow in terms of Q_F (measured forward flow). *Bottom.* Curves from patient 15, table 2. Arterial curve distinctly abnormal, but similar in contour to arterial curve of subject in heart failure without regurgitation (fig. 3*B*). Only by comparison with simultaneously recorded PA curve is it possible to interpret set of curves correctly as indicative of severe mitral regurgitation rather than typical of failure.

thereof, as used by Woodward and co-workers[15] or by Korner and Shillingford,[17] except that it is measured with respect to a "predicted" curve in the same individual. However, it alone does not discriminate between effects of volume, heart failure and other related parameters. Yet from a comparison of ΔAT and ΔMCT and from the difference, ΔT, a value is measured which, we believe, is primarily dependent on the regurgitant flow.

Upon introduction of a left ventricular bypass into the model, as seen in figure 7, a similar relationship can be readily demonstrated.

Calculations

Apparently, with use of the technics described and in the absence of regurgitation, by the time dye injected into the peripheral venous system reaches the PA, the curve inscribed is insensitive to subsequent dilution in volumes encountered in health or disease. This is not to say, however, that there is no mixing in the subsequent chambers. The observations simply indicate that the curve is not significantly changed by such further mixing.

Consider the case of regurgitation as the result of 2 extremes of flow, (a) the total flow (Q_T), and (b) the regurgitant flow (Q_R). In the intact organism, they cannot be determined directly. Recall that $Q_T - Q_R$ equals the net forward flow (Q_F). If any 2 can be determined the other can be calculated. Q_F can be obtained by the Fick principle; therefore, if either Q_T or Q_R can be described in terms of Q_F, quantitation of the regurgitation should be possible.

The total forward flow Q_T moves along the path of flow, and, since there is net forward flow, no matter how great the regurgitation, one may assume that some particles of the indicator will not be regurgitated but move along as a measure only of Q_T. Such a behavior characterizes the most rapid traversal possible for a given volume and is expressed by the difference in appearance times at the 2 sites, ΔAT. Thus equation I:

$$\Delta AT = \frac{\Delta V}{Q_T} \; ; \quad Q_T = \frac{\Delta V}{\Delta AT}$$

Q_F, the effective net forward output ($Q_T - Q_R$), on the other hand, is characterized by the time elapsed between the passage of the centroid of the dilution curve at each site. This is simply an application of calculation of forward flow-volume relation by the technic of Hamilton and his associates.[20] The measured

differences between the 2 curves are defined as ΔMCT. Then, equation 2:

$$\Delta MCT = \frac{\Delta V}{Q_F} \; ; \quad Q_F = \frac{\Delta V}{\Delta MCT}$$

If one now assumes that the volume traversed by the fastest moving dye (which gave Q_T) is equal to the volume traversed by the average particle (which gave Q_F), the equality of ΔV in equations 1 and 2 is established. Recalling that $Q_R = Q_T - Q_F$, equation 3:

$$\frac{Q_R}{Q_F} = \frac{\frac{\Delta V}{\Delta AT} - \frac{\Delta V}{\Delta MCT}}{\frac{\Delta V}{\Delta MCT}} =$$

$$\frac{\Delta V \; (\Delta MCT - \Delta AT) . \; \Delta MCT}{\Delta V \; . \; \Delta AT \; . \; \Delta MCT} =$$

$$\frac{\Delta MCT - \Delta AT}{\Delta AT}$$

which states that the ratio of regurgitant to net forward flow can be determined from the differences of 2 dye-dilution curves.

The ΔV used in these equations needs further definition because the assumed identity of ΔV in equation 1 and equation 2 may not be readily apparent. We have chosen a sample in equation 1 which escapes regurgitation; it is made up of smaller samples which may have taken various pathways (of nearly equal transit time) through a given volume between the 2 sites. The only requirement made of these particles is that they move only forward through this volume. In equation 2 the volume is the same, but the particles of indicator may traverse it only once or many times (as in regurgitation). The average traversal time yields the net forward flow through the volume between sampling sites. There is no reason why ΔV should not be the same in both equations.

These calculations allow a quantitative expression of the regurgitation in per cent of the forward flow. The model demonstrates that these calculations agree well with a known degree of shunting under the circumstances (fig. 7). Table 2 and figures 6 and 8 have used these calculations for quantitating the degree of regurgitation in human subjects.

Discussion

The foregoing method has been developed for quantitating valvular regurgitation relatively simply with little danger to the patient and by the use of commonly available technics.

It was thought that 2 dye curves being inscribed simultaneously, one proximal and one distal to the regurgitation, the effects of flow and volume on the one hand and of regurgitation on the other could be determined separately. This method yielded the information that, once a dilution curve is established in the nonregurgitant human subject (that is to say, once passage through the first mixing chamber has occurred), the effects of subsequent chambers cannot be discerned. This constant finding in a variety of flow and volume situations, with various combinations of chamber enlargement but in the absence of regurgitation, allows the use of the proximal PA curve as an internal "control" against which the effects of regurgitation further "downstream" may be checked. The essential identity of curves sampled from PA and from a peripheral arterial site has also been noted by others.[24, 25]

The comparison of 2 dye curves in regurgitation then suggested that some quantitation might be possible. The ratio obtained from equation 3 cannot be tested easily in the intact organism, though correlation of estimated regurgitation at surgery was good. This is not considered as support for the method but rather a lack of adverse evidence. In 3 cases, table 2, patients 4, 7 and 13, and figure 6(*top*), the degree of mitral insufficiency was thought to be minimal or virtually absent by clinical criteria, but at surgery a degree of regurgitation through the mitral valve compatible with the predicted amount was found.

It is possible to consider an individual with a left-to-right shunt within the central circulaton, such as may occur in patent ductus arteriosus as a form of left ventricular regurgitation. By sampling mixed blood proximal and distal to such a shunt, the present method could be checked against shunt estimations derived by the Fick principle of using "mixed" venous blood from areas involved in the shunt

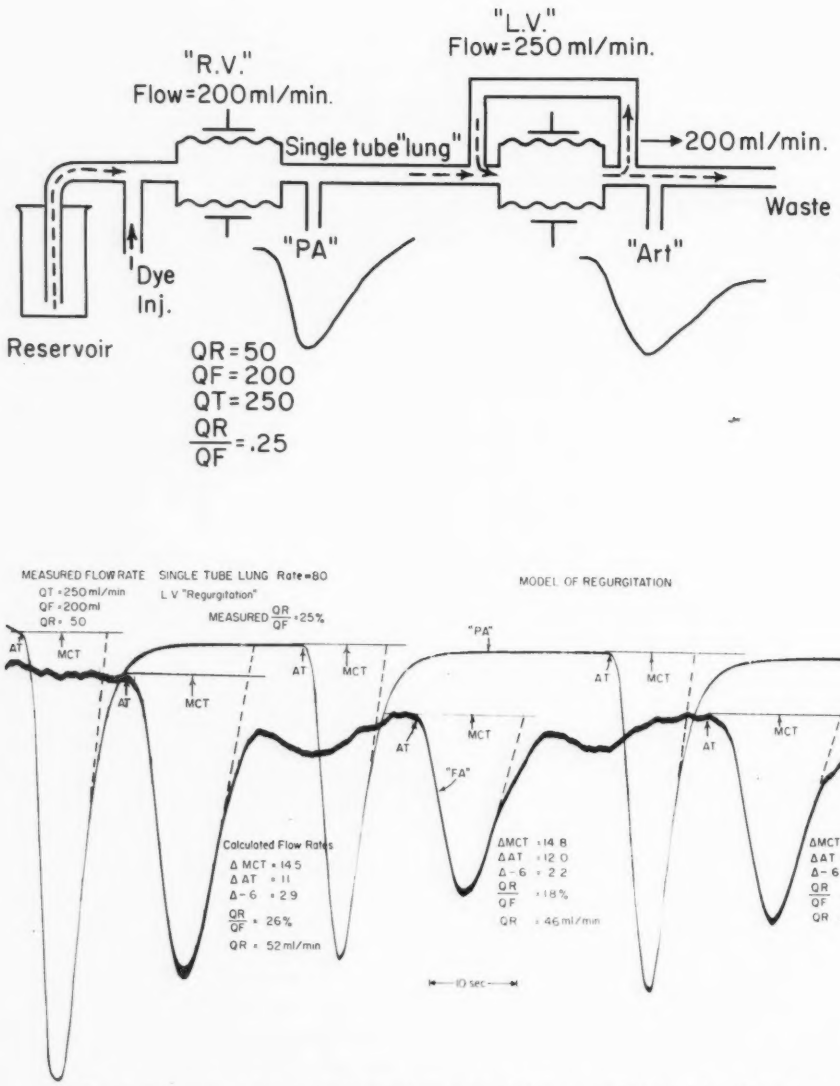


FIG. 7. Diagram of a "regurgitation" model and dye curves obtained by this arrangement. The left ventricular bypass (50 ml./min.) represents regurgitant flow (Q_R). Representative dye curves are sketched below each ventricle. *Lower figure.* Actual dye curves from model with total flow (Q_T) of 250 ml./min. and measured regurgitation (Q_R) of 50 ml. Three sets of dye curves shown, with calculated Q_R of 52, 46 and 52 ml. respectively.

vs. "unshunted" venous blood. Two patients were selected who had uncomplicated patent ductus arteriosus and in whom mixing of shunted blood seemed fairly constant in various branches of the pulmonary artery. Dye curves were recorded from the right ventricle and from the femoral artery and also from the main PA and femoral artery. "Regurgitation" (left to right shunt) was estimated by dye curves 60 per cent and by oxygen anal-

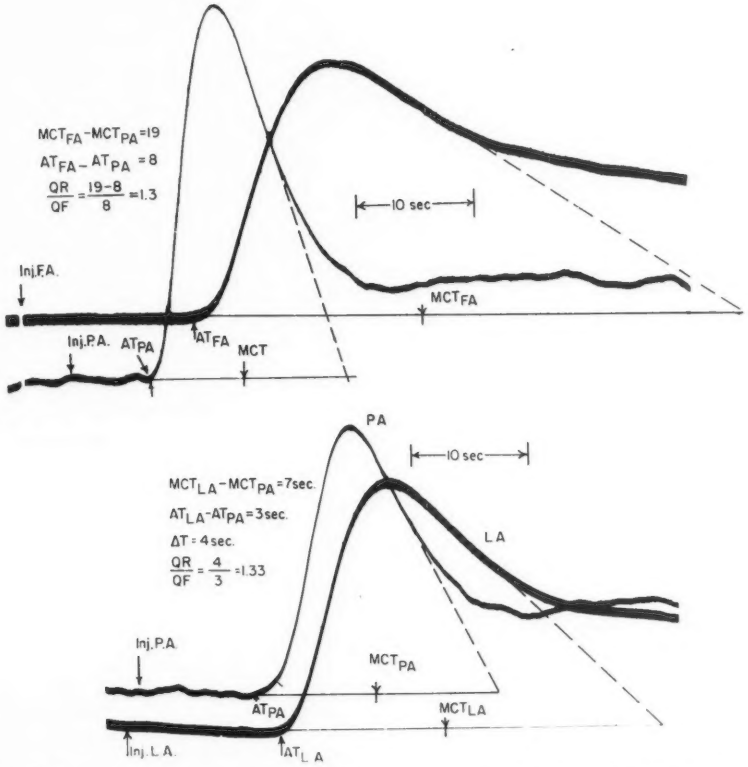


FIG. 8. Top curves from patient 21, table 2 with mitral stenosis and mitral insufficiency and fixed cardiac output. Comparison of PA and FA curves (*upper record*) show calculated regurgitation of 1.3 forward flow. Below are curves from PA and LA with presumably same cardiac output. PA curves of both records nearly identical, suggesting equal rates of net forward flow. However (*lower curves*) difference between LA and PA curves is much less striking than in *upper tracing*. The calculated Q_R/Q_F, however, is same in both sets because of proportionate decrease of both ($\triangle$MCT—$\triangle$AT) and $\triangle$AT. This supports assumption that in the regurgitant segment multiple sampling sites would show that the most rapid rate and the average rate of movement of indicator substances observe a constant ratio. Equation 3 may therefore be applied to any 2 sites in system. (Indocyanine Green, 5 mg., i.v.)

ysis 48 per cent in one, and 38 per cent and 32 per cent respectively in the second case (Table 3).

Another internal check is provided if the sampling site of the distal curve is moved, for instance from LA to FA. Naturally, the appearance time AT is later in the FA curve than in the LA curve, and ΔAT of equation 3 will be larger. If the ratio Q_R/Q_F measures insufficiency, it must remain constant, since it should not be influenced by the sampling site. ΔMCT $-$ ΔAT of equation 3 must therefore increase if the distal sampling site is moved farther downstream. Figure 8 indicates that this is clearly the case.

Using the method of Korner and Shillingsford, we found poor agreement with our own estimation, the method of the British investigators yielding consistently higher values for regurgitation than our own (fig. 9). The recent experimental approach of Sarnoff and his associates,[26, 27] might offer an independent check on these methods, and will be the subject of further investigations.

TABLE 2.—*Mitral or Aortic Regurgitation with and without Heart Failure*

Patient	Name	Age	Sex	Diagnosis	Failure	ΔMCT (sec.)	ΔAT (sec.)	ΔT (—.6) (sec.)	Q_R Q_F	Q_F (Fick) L. min.	Q_R L. min.	Q_F L. min.
1	E.W.	19	M	AI	0	16.7	10.2	5.9	.58	7.9	4.60	12.5
Interpolating LA values from PA curve						(13.7	7.2	5.9	.82	7.9	6.50	14.4
2	C.D.	37	M	MS Sl MI	4+	19.2	16.0	2.6	.16	3.2	.50	3.7
3	L.D.	29	F	AI MI	2+	30.3	17.0	12.7	.75	2.6	2.00	4.6
4	E.S.	23	F	MS MI	0	14.9	11.0	3.3	.21	4.0	.80	4.8
5	L.C.	33	F	MS MI	0	11.7	8.3	2.8	.34	3.3	1.10	4.4
6	B.W.	30	M	MS, MI AI	4+	33.6	17.0	16.0	.94	2.8	2.70	5.5
7	K.L.	34	M	MS MI	0	14.2	9.5	4.1	.43	4.0	1.70	5.7
8	T.H.	33	M	MS AI	0	12.5	10.0	1.9	.19	4.5	.90	5.4
Interpolating LA values from PA curve						(9.5	7.0	1.9)	.25	4.5	1.10	5.6
9	G.H.	46	F	MS MI	2+	15.2	11.6	3.0	.26	2.6	.60	7.2
10	A.C.	31	M	MS MI	4+	19.0	11.0	7.4	.67	3.8	2.60	6.4
11	G.L.	19	M	AI	0	8.5	6.0	1.9	.32	8.5	2.70	11.2
Interpolating LA values from PA curve						(5.5	3.0	1.9	.66	8.5)	5.60	14.1
12	R.H.	45	F	MI	2+	32.8	21.0	11.2	.53	2.5	1.30	3.8
13	W.J.	42	M	MI MS	1+	25.0	19.0	6.4	.34	3.4	1.20	4.6
14	F.H.	29	F	MS MI	4+	35.0	11.6	23.4	2.10	2.1	4.40	6.5
15	L.W.	19	F	MI MS	4+	19.6	9.0	10.0	1.10	2.0	2.20	4.2
16	O.A.	31	M	AI Sl MS	0	15.0	10.0	4.6	.46	6.0	2.70	8.7
17	H.M.	28	M	MS MI	0	21.0	14.0	6.4	.46	4.2	1.90	6.1
18	L.V.W.	39	F	MS MI	3+	23.0	14.0	8.4	.60	2.0	1.20	3.2
19	L.O.	11	M	MI MS	4+	33.0	14.8	17.6	1.12	1.8	2.00	3.8
20	L.W.	57	F	MS MI	2+	16.0	12.0	3.4	.28	2.9	.80	3.7
21	B.L.	14	F	MI MS	4+	19.0	8.0	10.4	1.30	3.6	4.60	8.2
				LA and PA		7.0	3.0	4.0*	1.33			
22	L.R.	47	F	MS	0	13.2	10.0	2.6	.26		1.30	6.3
				MI		13.0	10.0	2.4	.24	5.0	1.20	6.2
				LA and PA		8.7	7.0	1.7*	.24		1.20	6.2
23	M.C.	38	M	AS Sl MI	0	11.4	9.0	1.8	.20	5.4	1.10	6.5

(Continued on next page)

TABLE 2.—*(Continued)*

Patient	Name	Age	Sex	Diagnosis	Failure	ΔMCT (sec.)	ΔAT (sec.)	ΔT (—.6) (sec.)	Q_R/Q_F	Q_F (Fick) L./min.	Q_R L./min.	Q_T L./min.
24	J.B.	44	M	MS MI	0	11.4	7.5	3.3	.44	5.9	2.30	8.2
25	H.P.	39	F	MS MI	2+	15.0	12.0	2.4	.20	3.2	.70	4.0
				(LA—PA)		8.5	7.0	1.5*	.20	3.3	.70	4.0
26	B.H.	18	F	MS Sl MI	0	11.5	9.0	.9	.10	6.0	.60	6.6
27	D.O.	39	M	Sl MI O MS	0	16.1	12.0	3.5	.28	6.2	1.70	7.9
				(LA—PA)		9.3	7.0	2.3*	.33	6.2	2.00	8.2
28	G.W.	29	M	MI AI	2+	25.7	15.0	10.1	.67	4.3	2.90	7.2
				(LA—PA)		12.0	7.0	5.0*	.71	4.3	3.10	7.4
29	B.D.	51	F	MS Sl MI	4+	14.4	12.0	1.8	.15	4.7	.70	5.4
30	R.B.	28	M	MS MI	4+	19.8	13.0	6.2	.48	3.6	1.80	5.4
				(PA—LA)		15.4	10.0	5.4*	.54	3.6	1.90	5.5
31	D.C.	23	M	AS AI	0	10.7	9.0	1.1	.12	10.8	1.30	13.0
Interpolating LA values from PA curve						7.7	6.0	1.1	.18	10.8	1.90	13.7

*With left atrial and pulmonary artery sites, no correction of ΔT was made.

AI, aortic insufficiency
MS, mitral stenosis
MI, mitral insufficiency
LA, left atrial
PA, pulmonary artery

The method, of course, suffers from errors possible in all dilution technics that have recently been reviewed by Dow.[20] These mainly are related to the presence of short segments of laminar flow, the response time of the recording instrument and the possibility of alteration of flow during a given curve. Specific factors peculiar to our modification deal with the accurate recording of true appearance time at the 2 sites; conceivably the more sensitive instrument will record an earlier AT but this is seldom likely to be more than a fraction of a second. Equation 3 suggests that all errors in measurement diminish in importance with an increase in the absolute value of the denominator, ΔAT; thus, with high flow rates, accuracy may be less than at low flow rates. Besides, for accuracy, the no regurgitant curve should be obtained from a site extremely close in time to the regurgitant receptacle. In the case of mitral regurgitation the PA site is probably less than a second in time from the LA, which receives the regurgitation, and therefore introduces a small systemic error which decreases as the denominator of equation 3 increases. This is insignificant, as indicated by the consistently close agreement between the fraction of regurgitation as estimated from PA and LA curves (with a ΔAT of only a few seconds) and from PA and FA curves with a ΔAT considerably increased (table 2, patients 21, 22, 25, 27, 28, 30).

In aortic regurgitation, the distance of the PA site from the regurgitant system may be more important, and either the LA should be used as the proximal site or, if this is not possible, the PA curve should be shifted for-

TABLE 3.—*Patent Ductus Arteriosus*

Patient	Name	Dye Q_R/Q_F	Direct gas analysis Q_P/Q_F	Q_F	Q_{L-R}	Q''_R	Q_P	Q_T
1	R.C.	.60	.48	6.0	3.0	3.6	9.0	9.
2	M.A.	.38	.31	5.4	1.7	2.0	7.1	7.

Two cases of patent ductus arteriosus as a special form of "regurgitation." There is reasonably close agreement between values obtained by direct blood gas analysis and the degree of "regurgitation" predicted from the dye method.

Q_F = Fick output, systemic.
Q_{L-R} = L — R shunt from blood gas data.
Q''_R = "Regurgitant" flow — L — R shunt by dye method.
Q_P = Pulmonary flow from blood gas data. (Should equal Q_T from dye method.)
Q_T = Total flow (pulmonary flow from dye method).

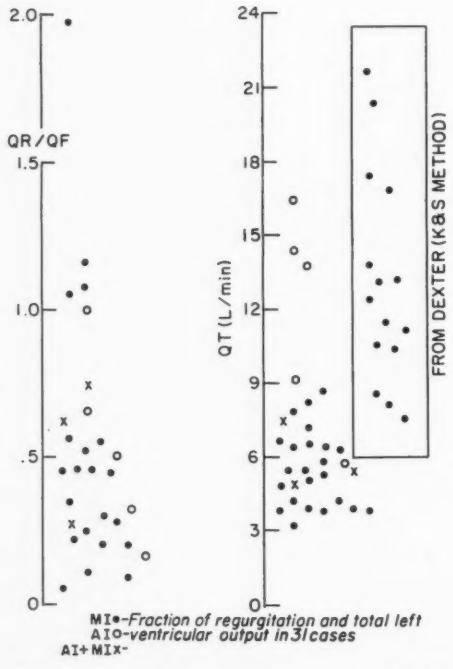


FIG. 9. 31 cases of single or multiple left-sided valvular regurgitation. In mitral insufficiency total left ventricular output (Q_T) seldom over 7 L./min. although Q_R/Q_F may exceed unity. This in contrast to results obtained by Korner-Shillingford application to similar group reported by Dexter and co-workers.[27] Q_T in aortic insufficiency is quite large, although Q_R/Q_F is relatively small in this group.

ward an appropriate time interval (usually 2 to 3 seconds).

The method applies equally well to mitral and aortic regurgitation, although, in the latter, proximal sampling from LA seems preferable to sampling from the PA site (for reasons mentioned). There is some information also concerning the differential quantitation of simultaneous mitral and aortic regurgitation. For this, 3 dye curves obtained from PA, LA and FA are needed. The difference between PA and LA curve indicates the degree of mitral, the difference between LA and FA, of aortic incompetence. Further data, however, are needed to clarify these relationships. Patient 28, table 2, is an example of such a case.

SUMMARY

1. A method has been described that attempts to quantitate valvular regurgitation on the basis of 2 simultaneously recorded dye-dilution curves, one sampled from the pulmonary artery and one from the arterial circulation.

2. With this technic in normal subjects and in patients with heart disease without regurgitation, the 2 curves are nearly identical in spite of the variable volume present between the proximal and distal sampling sites.

3. In regurgitation, the distal curve is altered, and by comparing the differences in

appearance times and in mean circulation times in the 2 curves the ratio of regurgitant to nonregurgitant flow may be obtained.

The calculated value agreed with surgical estimations and other independent internal checks. A simple hydraulic analog demonstrated that the calculated values agreed with the known forward and regurgitant flow.

The method is simple and appears adequate to separate mitral from aortic regurgitation when these occur in combination.

Acknowledgment

The authors are particularly indebted to Mr. Robert P. Carlisle for his invaluable technical assistance.

Summario in Interlingua

1. Es describite un methodo que viso a quantitar le regurgitation valvular super le base del registration simultanee de 2 curvas de dilution tinctural, le un ab le arteria pulmonar e le altere ab le circulation arterial.

2. In subjectos normal e in subjectos con morbo cardiac sin regurgitation le curvas producite per le methodo es quasi identic in despecto del differentias de volumine inter le sito proximal e le sito distal.

3. In casos de regurgitation, le curva distal es alterate, e per comparar le differentias inter le 2 curvas quanto al tempore del apparition e quanto al tempore circulatori medie, il es possibile obtener le proportion inter le fluxo regurgitante e le fluxo non-regurgitante.

4. Le valores assi calculate se trovava de accordo con estimationes chirurgic e con altere independente estimationes interne. Un simple analogo hydraulic demonstrava que le valores calculate esseva de accordo con le cognoscite magnitude del fluxo in avante e del fluxo regurgitante.

5. Le methodo es simple e pare esser adequate pro separar regurgitation mitral ab regurgitation aortic quando le duo occurre in combination.

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The Ballistocardiogram in Juvenile Diabetes Mellitus

By Robert E. Rakel, B.S., Thomas G. Skillman, M.D., and John R. Braunstein, M.D.

Ballistocardiographic studies were made in 41 patients with diabetes since childhood. A high incidence of abnormalities was observed. The possible diagnostic and prognostic implications are discussed.

THE high incidence of arteriosclerosis in juvenile diabetes is well known. White recently reported that 88 per cent of her large series of 1072 cases had evidence of calcified arteries after 29 years of diabetes.[1] It is evident that today vascular disease is the most important pathologic complication of the young diabetic, and that coronary atherosclerosis plays a significant part in this picture. The purpose of this report is to describe the ballistocardiographic abnormalities found in the course of juvenile diabetes mellitus. The high incidence of these abnormalities suggests the use of this tool as a possible aid in the early diagnosis of coronary sclerosis.

Method of Study

The 41 patients comprising the group attended the Juvenile Diabetic Clinic at the Cincinnati General Hospital. All patients experienced the onset of diabetes prior to the age of 15. The mean duration of diabetes was 17.4 years, with a range of 10 to 30 years. The mean age of the group was 24.2 years, with a range of 15 to 43 years. No patient had evidence of cardiac failure. Rheumatic or congenital heart disease was not believed to be present in any case, as evidenced by history, physical examination, roentgenologic or electrocardiographic study. No patient was obese.

Ballistocardiograms were made with the patient fasting and in a rested state. The tracings were recorded on a high-frequency table-type research instrument[2] that recorded both head-to-foot and side-to-side movements. Lead I of the electrocardiogram was recorded simultaneously on the same paper for means of coordination. Following the ballistocardiogram a standard 12-lead electrocardiogram was taken. For control data, 41 normal subjects of the same age and sex distributions were studied. The ballistocardiograms were studied for abnormalities in pattern and amplitude.

On the day of examination other studies were conducted of factors that might influence the ballistocardiogram. A complete physical examination was carried out. Roentgenologic study of the aorta and peripheral vessels was made for calcification. The fundi were examined by an ophthalmologist. The concentrations of blood sugar, serum total lipids and serum cholesterol were determined.

Results and Discussion

Of the 41 patients studied, 17 (41 per cent) had abnormal ballistocardiographic patterns. Many were persistently abnormal in serial tracings taken at yearly intervals. No irregularities were found in the control group. The abnormalities found are listed in table 1. It is apparent that no single pattern predominated, and that more than 1 abnormality was usually present in a single tracing. Only 2 of the entire group of 41 patients had abnormal electrocardiograms. These 2 also had abnormal ballistocardiograms. The electrocardiographic pattern in these instances was compatible with left ventricular ischemia. The amplitudes of the complexes were also measured and compared to the criteria of normal, as determined by Starr.[3] All normal tracings had normal amplitudes. Of the 17 abnormal tracings 12 were abnormally small and 5 were within normal limits in amplitude.

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TABLE 1.—*The Abnormal Ballistocardiographic Patterns in 17 Cases of Juvenile Diabetes*

Type of Abnormal Pattern	Times Observed
Abnormally small complexes	8
Increased transverse component	7
Late downstroke pattern	6
Increased respiratory variation	5
Early M pattern	4
Deteriorated complexes	3

In comparison of the general characteristics of the group giving normal tracings with those with abnormal tracings, no significant differences between ages, sex distributions, duration of diabetes or insulin dosage (table 2) were found.

Attempts were made to relate the ballistocardiographic changes to demonstrable vascular complications (table 3). The patients were too few to show a significantly higher incidence of retinopathy or peripheral vessel calcification. However, the incidence of arterial hypertension (sustained pressure in excess of 140/90) was significantly greater in those with abnormal ballistocardiographic patterns ($p < 0.02$). Hyperlipemia or hypercholesterolemia was not more significantly frequent in those with abnormal tracings. The mean concentrations of blood glucose were equivalent in the 2 groups.

TABLE 2.—*General Characteristics of the Patients with and without Abnormal Ballistocardiographic Patterns*

	Normal pattern (24)		Abnormal pattern (17)	
Mean age				
Years	22.6		26.4	
Range	(15-32)		(17-43)	
Sex	12 M	12 F	7 M	10 F
Mean duration of diabetes				
Years	16		19	
Range	(10-27)		(10-30)	
Mean daily insulin dosage (units)	73		61	

Since the observations were made, 3 of the patients have died, all of whom had abnormal tracings. Autopsies performed on 2 demonstrated marked coronary atherosclerosis and interstitial fibrosis of the myocardium.

Because hyperlipemia has been reported to influence the ballistocardiogram,[4] 4 of the patients with abnormal tracings and elevated serum lipids were studied serially at 15-minute intervals for 1 hour after the intravenous injection of 100 mg. of heparin. Two patients with normal ballistocardiograms and elevated serum lipids were also given heparin and served as controls. No alterations were found to follow heparin administration in either group.

From the above observations it appears that the abnormal ballistocardiographic findings were more prevalent in those with hypertension. It is most likely that the abnormalities were related to the development of coronary sclerosis. The prevalence of such sclerosis is well known in the course of juvenile diabetes. Accordingly, it is possible that the ballistocardiogram will be an aid in the early diagnosis of coronary sclerosis in juvenile diabetes.

SUMMARY

Ballistocardiograms were made from 41 patients with juvenile diabetes of more than 10

TABLE 3.—*The Incidence of Vascular Complications and Abnormal Concentrations of Blood Constituents*

Abnormalities	Pattern	
	Normal (24)	Abnormal (17)
Diabetic retinopathy	13	15
Arteriosclerotic retinopathy	7	9
Peripheral vessel calcification	5	6
Hypertension (>140/100 sustained)	1	7
Serum lipids > 900 mg. %	12	13
Serum cholesterol > 250 mg. %	0	2
Blood glucose concentration		
Mean	196	200
Range	(88-332)	(58-480)

years' duration. Seventeen (41 per cent) had abnormal patterns, 2 of whom also had abnormal electrocardiographic patterns. It is suggested that the abnormalities were related to the early development of coronary sclerosis.

Summario in Interlingua

Ballistocardiogrammas esseva obtenite ab 41 juveniles con diabete de plus que 10 annos de duration. In 17 (41 pro cento) le configurationes ballistocardiographic esseva anormal. In 2 del 17, etiam le configurationes electrocardiographic esseva anormal. Es opinate que le anormalitates esseva le effecto de un disveloppamento precoce de sclerosis coronari.

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Elevation of serum oxalacetic transaminase is not specific for any particular disease but depends upon a number of factors contributing to serum transminase levels. On the other hand, glutamic-pyruvic transaminase is said to be more specific for detection of hepatocellular damage and less sensitive as an indicator of myocardial necrosis. The serum concentrations have been correlated with the enzyme concentrations in the respective tissues involved. In this report, the sera of 150 patients were compared with respect to oxalacetic and pyruvic transaminase activities to determine the value of the latter in a variety of disease states. In 24 patients with myocardial infarction the serum oxalacetic transaminase was elevated; pyruvic transaminase was elevated in some and normal in others. In patients with hepatic disease including hepatitis, cirrhosis, cancer, and hepatic necrosis and in acute pancreatic necrosis, both transaminases were elevated. Four of 5 patients with viral hepatitis had higher serum pyruvic transaminase than oxalacetic transaminase levels. The highest levels of activity were noted during the initial phase of viral hepatitis. In extrahepatic obstructive jaundice, both transaminases were elevated; slight elevations occurred in both serum enzyme levels in intrahepatic obstructive jaundice. These findings indicate that serum pyruvic transaminase is not more sensitive as an indicator of hepatocellular damage nor is it specific for this condition. The pyruvic transaminase assay should find its greatest use as an adjunct in the interpretation of an elevated oxalacetic transaminase level.

Shuman

Technic for Non-Surgical Insertion of Large Polyethylene Tubing into Blood Vessels

By CHARLES T. DOTTER, M.D., AND JOSEF R. SMITH, M.D.

QUITE independently of each other, the authors of this brief report developed a simple technic which, without the use of special equipment, allows the percutaneous insertion of large bore polyethylene tubing into blood vessels. Certain features have been used by others.[1-14]

It is self-evident that the rigid point of a hypodermic needle, though desirable for percutaneous insertion into blood vessels, constitutes an undesirable source of continuing vascular trauma thereafter. In our technic, the needle serves only to effect entry and guide the tubing into the vessel's lumen. An important difference from the usual approach is that *here* the tubing is inserted *around* rather than through the needle.

METHOD

Preliminary Preparation

The bore of the polyethylene tubing to be used determines the gage of the guide needle, since the latter must fit smoothly into the tubing. Polyethylene tubing is available in sizes suitable for use with all needle gages including the 12-gage Robb-Steinberg angiocardiography needle.

A 1-mm. lengthwise slit is made through one wall of the tubing 4 to 8 inches from one end. The tip of the needle is introduced through this slit, pointing toward the end of the tubing and the needle shaft advanced until the butt of the needle bears upon the tubing. At this juncture, there will be approximately 4 to 6 inches of tubing projecting beyond the tip of the needle. This is grasped by a hemostat and countertraction applied at the base of the needle shaft so as forcibly to stretch or draw out the tubing. This results in thinning of the wall of the tubing at and close to the tip of the needle. The stretched tubing beyond the needle is then cut off so as to leave the needle tip projecting slightly beyond the site of severance. A few trials will show that the foregoing preparations are simpler than their description. The needle and tubing may be prepared before or after sterilization; in either case, gloves will be necessary for the actual insertion into a blood vessel.

Insertion into Blood Vessel

Insertion is facilitated if, after procaine, a small (1-2 mm.) nick is made in the patient's skin over the desired vessel. If this is a vein, it should be distended through application of a tourniquet. When blood issuing from the needle indicates an intraluminal position of its tip, the needle and its surrounding jacket of tubing are advanced as far as possible within the lumen. The sensation of a resistance giving way may signify entry of the tubing into the vessel. Thereafter, the needle (alone) is removed, care being taken not to retract or otherwise dislodge the tubing in the process. Once the needle is out, the tubing is advanced as far as purpose dictates, and taped in place on the forearm. Arterial cannulation by this or any other method demands a higher degree of competence than venipuncture.

ADVANTAGES OF TECHNIC

This technic possesses several real advantages in addition to being fairly simple to perform. In eliminating the need for surgical exposure of the vessel to be cannulated, time is saved and the possibility of wound infection or vascular damage is reduced. Several other approaches to the problem have been reported, but these have been limited in one of 3 respects: 1. The widely used method[1-5] of threading a small tube through the lumen of a needle suffers in that the needle cannot be removed easily and a severe limitation is imposed on the size of tubing that can be used. Though in many instances small bore tubing suffices for the purpose of the intubation, larger caliber tubing is more durable and perhaps less apt to be the site of thrombus formation. 2. Certain reported procedures[6-13] though feasible require the use of

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FIG. 1. Technic for nonsurgical insertion of large polyethylene tubing into blood vessels. *A*. A few inches from one end of the tubing make a longitudinal slit just large enough to admit the needle. *B*. Push the needle into the tubing until the hub butts against the tube wall. *C*. Stretch the tube, as shown, until its elastic resistance is overcome. A little practice is better than a long description of how to do this. *D*. The stretched tubing moulds itself around the end of the needle, thinning near the tip. The projecting end of the tubing is then cut off through the thinned wall near the needle point to complete the preliminary preparation. *E*. The needle, as shown, is ready for insertion (with or without a syringe) into a vessel. The shoulder of tubing around the needle shaft shows at the arrow. Out of the picture to the right of the needle is the tubing to be advanced following insertion and removal of the guide needle. The principal advantage of this method over others is that the tubing length and caliber are limited only by the patient's anatomy rather than by the needle gage or other special equipment such as sounds.

special needles or sounds, not generally available. 3. Seldinger in a recent report[14] has used a method similar in many respects to ours, but limited in scope to lengths of tubing shorter than the shaft of the needle employed.

Our technic was developed to meet needs

encountered in connection with angiocardiography and special cardiopulmonary procedures, and here it has been of particular value. Angiocardiographic success demands the rapid delivery of a large volume of fluid into the right atrium, e.g., 50 ml. in 1.5 seconds in average adults.[15, 16] By advancing the tubing until its tip lies in the superior vena cava, the dose may be delivered rapidly to the right place and in an intact fluid bolus. This avoids the occasional failure of angiocardiography that results when a sustained Valsalva maneuver by the patient forces contrast agent up into the neck veins, thereby diluting and delaying the arrival of the contrast agent. If injection is made through tubing into the superior vena cava, the Valsalva maneuver is capable of producing an improvement in radiographic contrast by reducing temporarily the nonopaque blood reaching the right atrium. Knowledge of the length of tubing passed and localizing sensations felt by the patient during the rapid trial injection of cool saline eliminate the need for fluoroscopic localization. Unless pressure injection apparatus is used, the small bore of the usual cardiac catheter makes it useless for selective angiocardiography save where small doses suffice. Finally, when injection is carried out through tubing rather than a needle, the likelihood of painful extravasation is virtually eliminated.

In the realm of cardiopulmonary procedures, this technic is especially valuable in performing cardiac output studies by the dye-dilution technic. It is possible to obtain more complete and more central injection of the indicator agent, hence improving the technic,[17] without the necessity of a venous cut down.

Summary

A simple technic is presented for the nonsurgical insertion into blood vessels of large bore polyethylene tubing.

Acknowledgment

In addition to those covered in references 1 through 14, acknowledgment is given for helpful suggestions to one of us (J. R. S.) made by Dr. Giles G. Bole, Jr., of the Department of Medicine, University of Michigan.

Addendum

After this article was accepted for publication, a report[18] describing a similar technic was brought to our attention. The latter technic differs from ours in that the needle is not inserted through the wall of the polyethylene tubing. This means that the length of tubing cannot exceed the longest needle available, thus somewhat restricting the usefulness of the method. In other respects the two technics are essentially identical.

Summario in Interlingua

Es presentate un simple technica pro le insertion nonchirurgic, a in le vasos de sanguine, de tubos de polyethyleno a grande calibre.

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CLINICAL PROGRESS

The Effectiveness of Long-Term Treatment of Malignant Hypertension

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HYPERTENSION even of mild degree shortens life span. Thus Dublin, Lotka and Spiegelman[1] in 1940 stated, "mortality rises steadily and markedly with increasing elevations of both the systolic and diastolic pressures" and, "In the group with the highest blood pressures included in this [insurance] experience—and these are not considered seriously high by many clinicians—the mortality from cardiovascular renal disease was nearly 4½ times the average for all standard risks."

This actuarial experience has been supplemented by Bechgaard, Kopp, and Nielson,[2] who have followed the clinical courses of 1,038 out-patients with hypertension over periods of from 16 to 22 years. As compared with a normotensive group, the patients with hypertension, especially the men, showed decreased survival with increasing levels of pressure and, at the end of an average follow-up of 19 years, there survived only one fifth of the men and about half the women.

These impressive data on prognosis in hypertension should not obscure the fact that the outcome in individual cases of essential hypertension is highly unpredictable. Some patients, most of them women, may go through a normal or nearly normal span of life. However, a majority will die prematurely, not from hypertension or hypertensive vascular disease as such, but from complications of hypertensive and coronary heart disease, cerebrovascular damage or some other arterial (not arteriolar) catastrophe. Potent antihypertensive drugs have been in use for 7 to 8 years but with such a variable course and a lack of association between the cause of death and the extent of arteriolar damage it is impossible to assess therapeutic gains in such terms as prolongation of life or prevention of complications. To be convincing, such an evaluation must await a survey of very large numbers of patients over long periods of time.

The situation is quite different when we deal with the malignant (accelerated) phase of essential hypertension. The course of this hypertensive syndrome is well characterized, predictable and relatively brief, with survival of only 10 to 20 per cent of patients for 1 year.[3–6] Death is caused primarily by hypertensive arteriolar vascular damage. This is commonly expressed by malignant nephrosclerosis with rapidly progressive renal failure, by intracerebral hematoma, and not infrequently by uncontrollable cardiac failure. A survey of survival and causes of death among a group of patients suffering from this condition who have been under intensive treatment with potent antihypertensive agents available during the past 7 years, should establish the beneficial effects of these agents in terms of prolongation of life. Further, these drugs act in various ways to effect their common denominator of decreased arterial pressure. Hence, such a survey might also delineate those aspects of the vascular disease

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TABLE 1.—*Calculation of the Severity Index**

Datum	Units Assigned				
	0	1	2	3	4
Diastolic pressure, average	95 or<	96-110	111-125	126-140	140
Cardiac (American Heart Association classification)	0	I	II	III	IV
Renal					
Proteinuria (Gm./24 hr.)	0.2 or<	0.2-0.5	0.51-1.0	1.1-3.0	>3.0
Serum creatinine (mg./100 ml.)				1.5-3.0	>3.0
Cerebral					
Fundi (Keith-Wagener)	0	I	II	III	IV
Signs	0	0	Severe headache	Old stroke	Encephalopathy or fresh stroke

*Where a panel is graded by 2 components the sum of the estimated units is divided by 2 to establish the value for that panel.

of malignant hypertension that are pressure-dependent and indicate some that may have no direct association with arterial pressure level as such.

This report therefore has a 2-fold aim: (1) to show the effect of treatment with potent antihypertensive drugs on survival in a group of patients with malignant hypertension, and (2) to evaluate the extent to which the height of the blood pressure is a factor in the complications supervening during its treatment.

EVALUATION OF THE SEVERITY OF VASCULAR DISEASE

Comparative or critical study of the value of treatment in hypertensive disease demands careful, systematic assessment of the severity and extent of that disease prior to treatment, followed by sequential, similar estimates during treatment. While this applies to the individual patient, averages of these estimates—if they fall within a fairly narrow range—can then apply to comparisons between groups. It is not enough to describe a patient or patient group as suffering from malignant hypertension. It would be misleading to compare results of treatment between patients in whom vascular disease had just begun and those in whom vascular damage was extensive. Further, it is desirable to have some systematic way of associating observed blood pressure levels with the other manifestations of the hypertensive syndrome. Lastly, a means of expressing the course of the disease in simple numerical terms is particularly useful at the present time. Although it is well recognized that antihypertensive treatment can control some of the more acute aspects of severe hypertensive disease effectively and promptly, we know little of the "natural history" of treated malignant hypertension.

To serve these purposes we have used a numerical Severity Index based on objective estimates made in the more accessible vascular beds. The mode of calculation of this index is indicated in table 1 (table modified from reference 7). A maximum of 4 points is allotted to each of 4 panels of cardiovascular status; these are, respectively, average of supine diastolic pressure, and estimates of circulatory status in the cardiac, renal, and cerebral vascular beds. The sum of the grades from the 4 panels considered constitutes the Total Severity Index. For example, a patient with a supine diastolic average between 95 and 110 mm. Hg but no objective indication of vascular changes in the other panels would be graded as having a Total Severity Index of 1, while a patient with a diastolic average greater than 140 mm. Hg severe cardiac failure, retinal hemorrhages, exudates and papilledema, hypertensive encephalopathy, and severe azotemia, would have a total score of 16. This index is used in the description of clinical courses and mortality that follows. The diastolic blood pressure averages used in the sequential estimates during treatment for the most part were obtained from daily meas-

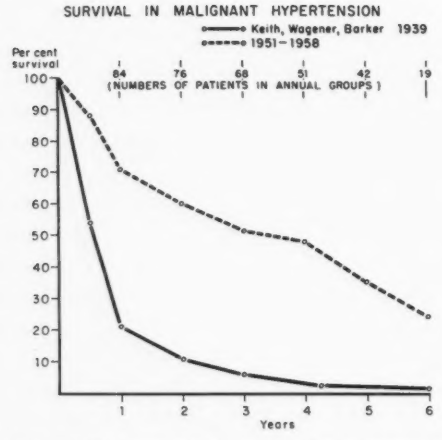

FIG. 1. The survival of treated hypertensive patients (1951-1958) as compared with a group of untreated patients (Keith, Wagener, Barker, 1939).

urements taken at home by the patient or a member of his family.

PATIENT GROUP

The group under consideration consists of 84 patients, 56 men and 28 women of an average age of 46 years, who presented the syndrome of malignant hypertension. The period of the study was from January 1, 1951, to January 1, 1958. We have included only those who survived for a minimum of 3 months from the time the diagnosis was established. The period of observation extends from this minimum to nearly 7 years. In 75 of the 84 the disease process was considered to be the malignant phase of essential hypertension, in 5 it was associated with chronic pyelonephritis and in 4 with occlusive lesions of major renal arteries. These last 4 were treated by nephrectomy, and in 3 hypertension and vascular disease remitted. Eighty-one patients, including the 1 patient in whom nephrectomy was of no benefit, were treated with 1 or more of the available potent antihypertensive drugs, singly or in combination.

SURVIVAL

During this period of 7 years, 52 of the 84 patients died. This over-all mortality (62 per cent) is at first glance discouraging. However, the obverse is that 32 per cent survived. This datum is encouraging indeed to all acquainted with the course of untreated or ineffectively treated malignant hypertension, whether from personal experience or from the reports of Keith, Wagener, and Barker,[3] Page,[4] Schoenstaedt and Sokolow,[5] Kincaid-Smith, Mac-Michael and Murphy,[6] and others. Among these reports, the later ones bear out in general the experience of Keith, Wagener and Barker, and their earlier estimates of survival will be used for simplicity's sake as indicative of the course of malignant hypertension prior to the use of potent antihypertensive drugs.

Keith, Wagener and Barker reviewed clinical courses of 146 patients who presented themselves with severe hypertension, retinal hemorrhages, exudates and papilledema, and usually other symptoms of diffuse, rapidly advancing arteriolar disease. Some 20 per cent of the these patients survived for 1 year and, very significantly as concerns the present survey, only 1 survived 5 years or more; in general, experience has been that most such patients are dead or wholly disabled by the end of 1 or 2 years and that all—with rare exceptions—are dead at the end of 4 or 5 years.

Figure 1 shows a comparison of survival rates in the Keith, Wagener and Barker group with the experience in our group of patients treated for malignant hypertension. The figure indicates that treatment causes a significant prolongation of life in many patients with malignant hypertension, although it does not prevent premature death in the majority. Certain reservations should be made as to the comparability of our data with those of Keith, Wagener and Barker. Their study covered a period of 5 years and followed the courses of 146 patients during this time. In contrast, not all of our treated group have been followed for 7 years, since we are dealing with patients who started treatment between January 1, 1951 and January 1, 1957. Thus we have followed 84 patients from 3 months to 1 year, but as the period of observation became longer the numbers of patients became progressively smaller, as indicated in figure 1. Our final estimate of survival is made from

about 7 years' experience with 19 patients. Secondly, as will be noted below, nearly a third of the first-year mortality in the total group was attributable to a complication of treatment (hexamethonium pneumonitis)[8] which we have not witnessed in recent years. Other factors than antihypertensive drugs, such as sodium restriction in congestive heart failure, the use of mercurials and of other supportive measures, may have altered the course of malignant hypertension in our patient group as compared with the group of Keith, Wagener and Barker. However, our former experience had shown us that these measures were nearly always ineffective and that even major procedures, such as sympathectomy or treatment with kidney extracts of pyrogens, usually evoked no more than a few months remission in the course of the disease. Hence we believe that the 2 groups of patients are initially roughly comparable and that the major difference between them is the use of antihypertensive agents in our group.

Analysis of Causes of Death

Previous reports by our group and by many others abundantly show that the syndrome of malignant hypertension is reversible by any procedure that results in prolonged lowering of diastolic pressure toward normal levels. This result has been accomplished largely by appropriate and intensive use of antihypertensive drugs, by restriction of dietary sodium by nephrectomy or other surgical procedures in patients with remediable renal hypertension, and by extensive lumbodorsal or dorsal sympathectomy. However, most such reports provide little information on prognosis over long periods, as concerns either survival or disability. In this regard, the data of figure 1 indicate that reversal of the syndrome of malignant hypertension—accomplished in practically all of the 84 patients—does not protect them against premature death from cardiovascular causes or, by inference, restore them to abundant health.

Of the 52 deaths, 8 were attributable primarily to interstitial pneumonia complicating treatment with hexamethonium. Median survival in this group of 8 was 5 months and all had died at the end of 8 months. While these patients as a group presented evidences of very severe disease prior to treatment, this complication of treatment probably distorts the survival data of the first year, since it accounts for one third of the first-year mortality. The influence of this unfortunate complication can be estimated by comparing mortality (24 of the 84 patients) among the total first-year group with mortality in 33 patients observed after January 1, 1954, when the use of hexamethonium had been discontinued. Among these 33 only 6 (18 per cent) died during the first year, whereas 9 or 10 deaths would have been anticipated. Hence, avoidance of pneumonitis seems to yield a definite gain in prognosis. We have no indication of the mechanism or pathogenesis of this complication.

It is exemplified by the course of a 44-year-old man who came with advanced malignant hypertension, heart failure and azotemia (serum creatinine 5.6 mg./100 ml.). With hexamethonium, lying diastolic pressures were maintained at about 110 mm. Hg, papilledema regressed, proteinuria decreased, and congestive failure was easily controlled. At the end of 3 months, he developed severe dyspnea, which decreased on lying down. This symptom was progressive, and during the course of 2 weeks he developed pulmonary consolidation and died of diffuse pneumonitis.

The most common (42 per cent) single cause of death was renal failure. This occurred in 22 patients and was present in severe degree in 2 patients whose proximate cause of death was myocardial infarction. Renal failure in the 22 patients followed two courses.

Nine patients showed rapidly progressive loss of renal function; of these 5 died within 6 months and all in less than 12. For example, a 28-year-old Negro woman had a diastolic pressure average of 165 mm. Hg, other signs of severe malignant hypertension, and adequate renal function (urea clearance of 40 per cent of normal and serum creatinine 1.7 mg./100 ml.). She was given chlorisondamine and mecamylamine. Blood pressure response was poor, with supine diastolic average

of 130 mm. Hg and modest decrease in standing blood pressure. Retinopathy diminished but renal function progressively deteriorated and the patient died at the end of 3 months in uremia.

In contrast to those who went rapidly into renal failure, the lives of 13 patients who died of slowly progressive renal failure seemed definitely to have been prolonged by treatment. These survived from 14 to 60 months and the median survival was 27 months. In all, treatment was begun when renal function was definitely impaired. In contrast with the former group, however, excretory function stabilized for long periods during treatment and only deteriorated during several months prior to death. For example, the blood pressure of a man of 51 years with malignant hypertension responded very well to treatment with hydralazine, which was started in April 1951. At that time urea clearance was 28 per cent of normal and blood urea 84 mg./100 ml. In September 1954, 3½ years later, blood urea was the same and creatinine was 2.7 mg./100 ml. However, in March 1955, 6 months later, azotemia had increased and serum creatinine had risen to 5.7, and in August 1955 to 11.5 mg./100 ml. He died in uremia 5 years after beginning treatment.

The remaining 22 deaths were attributable to complications of arteriosclerosis, presumably atherosclerotic. Among these were 13 instances of cerebral hemorrhage, 7 of myocardial infarction and 2 of ruptured aortic aneurysm. These catastrophes occurred at intervals of from 5 to 66 months of treatment. They showed no pattern of occurring early during treatment, as in patients succumbing to hexamethonium pneumonitis or rapidly progressive renal failure, or later in the course as in those with delayed or slowly progressive renal failure. By way of example we cite the case of a white woman of 49 years, whose intense malignant hypertension responded well to treatment with ganglion-blocking agents and was later controlled with reserpine. During the first 3 years of treatment supine diastolic was persistently less than 110 mm. Hg, but during the fourth year it rose to an average of 112 mm. Hg. At the end of the fourth year of treatment she died from a massive cerebral hemorrhage, having maintained fair health and productivity in the interval.

Considering the deaths associated with hexamethonium pneumonitis as accidental and not representative of present experience, we summarize by noting that 9 patients died of rapidly progressive renal failure, 13 of delayed or slowly progressive renal failure and 22 of complications of atherosclerosis. Death from rapidly progressive renal failure is the usual course of untreated malignant hypertension, and the clinical data in this group of 9 patients indicate that treatment caused no more than some attenuation of the progress of the disease. However, neither delayed or slowly progressive renal failure nor complications of atherosclerosis are characteristic of the untreated disease. Since these causes of death in the majority of patients differ substantially from the usual course of malignant hypertension, we conclude that treatment has significantly altered the evolution of this condition.

Initial Severity of Vascular Disease and Survival

It would be anticipated that treatment would be more successful in prolonging life and preventing complications in patients with recent malignant hypertension and minor evidences of diffuse vascular damage as compared with those in whom the process has been active for long periods and had resulted in extensive destruction of the circulation. This anticipation is supported by our data. The Total Severity Index in nonsurvivors averaged 10.4, whereas the average was 8.0 in the survivors. Grades of scoring in each panel of the Severity Index were higher among nonsurvivors with one exception. Averages of these panel grades respectively as between nonsurvivors and survivors were as follows: blood pressure 3.1 and 2.6; cardiac 2.3 and 1.7; renal 2.3 and 1.2; and cerebral 2.7 and 2.5. The exception in the cerebral panel suggests that this mean of estimate may be defective. Apparently retinopathy, which enters into this datum, i

not a valid index of the presence or extent of latent cerebrovascular damage. Among the differences, the greatest and most significant is the initial estimate of renal damage. This was definitely higher in nonsurvivors than in survivors. Thus, the data support the belief that prolonged survival during treatment is a function of the over-all initial severity of the disease and especially of the degree of initial renal damage. However, some azotemic patients—such as the one noted above who died of slowly progressive renal failure—have surprised us by surviving for months and years. During this time they have maintained their social and economic positions much to their own and their families' advantage. Hence, contrary to some physicians, who seem to advocate withholding treatment in patients with severe hypertension and azotemia, we believe that there is little to lose and much to gain by undertaking treatment in all but the desperate circumstances.

Arterial Pressure and Survival

The control of blood pressure during treatment was considered "good" if the supine diastolic average was persistently less than 110 mm. Hg. Some patients whose responses were good at first later became resistant to treatment, so that control was "poor" during a large part of the treatment period. For simplicity's sake, these latter are considered here to have shown poor responses throughout.

First, we could establish no association between the occurrence of hexamethonium pneumonitis, the doses of drug used and the estimate of blood pressure control; this complication occurred, however, in patients with severe disease who showed some azotemia.

Among the 9 patients with rapidly progressive renal failure there were only 2 whose blood pressure control was considered good while poor responses were observed in the other 7, who also showed no more than a modest blood pressure fall when standing. However, even this slight degree of blood pressure control may be significant, since none of those with rapidly progressive renal failure who came to autopsy showed the florid and diffuse necrotizing renal arteriolar lesions characteristic of untreated malignant hypertension. Rather, the lesions were discrete and attenuated, being more productive than inflammatory in appearance.[9]

Among the 13 patients with slowly progressive renal failure as a primary cause of death, there were 7 whose control was considered good and 6 in whom it was listed as poor. Apparently, in this group, the adequacy of blood pressure control is a less significant determinant of course than in those with rapidly progressive renal disease. Rather, the significant factors in this condition seem to be the extent and severity of the disease at the time treatment started and in particular the initial severity of renal disease.

The next major cause of death was cerebral hemorrhage. Among 13 patients who died of this complication 10 showed poor control and 3 good control. Control of supine diastolic pressure at levels under 110 mm. Hg therefore significantly reduces the risk of this complication. There were 7 patients who died of myocardial infarction, 2 of whom had slowly progressive renal failure. In this small group myocardial infarction did not show an association with blood pressure control; it occurred in 5 with good and 2 with poor responses to treatment.

In brief, rapidly progressive renal failure and cerebral hemorrhage in treated malignant hypertension show an association in their incidence with poor control of blood pressure. Clinical and pathologic evidence suggests that the modest fall in standing blood pressure provoked by treatment in patients with poor control did attenuate the severity of vascular disease. In contrast, the occurrence of 2 other major complications, slowly progressive or delayed renal failure and myocardial infarction, showed no close association with levels of supine diastolic pressure during treatment, which were often classed as good.

This last observation suggests that there may be some unusual characteristic of the renal and coronary vasculature of patients with treated, even well-treated, malignant hypertension. The coronary vascular lesions

have not been reviewed in detail. However, the renal vessels have been studied carefully,[9] and these show remission of all or most aspects of the necrotizing arteriolar lesions of malignant hypertension in patients with apparently good control. However, the larger arteries—major branches, arcuates and interlobar arteries—exhibit a diffuse fibrous intimal hyperplasia that is sometimes occlusive. It is this productive, arterioselerotic lesion that seems to be the cause of the syndrome of slowly progressive renal failure. This arteriosclerotic renal lesion, like myocardial infarction, apparently can develop in spite of good blood pressure control. Hence it may be that the fatal myocardial infarcts that occurred during treatment are attributable to similar diffuse intimal lesions developing in the coronary vessels.

This demonstration of an unusual type of arteriosclerotic lesion in the large renal vessels of patients with treated malignant hypertension poses several problems as to its nature. First, it might be supposed that this is a delayed reaction to damage done mechanically to larger arteries or done by lipid "infiltration" during the course of the malignant hypertension prior to treatment. However, there is no convincingly direct evidence that this is the case. Alternatively, this process may represent mitigation of a basic process, which in the absence of control of blood pressure is expressed primarily in arteriolar damage and necrosis, and with control of blood pressure, by intimal fibroplasia in larger vessels. On the latter assumption, it would seem that toxic, humoral factors may contribute to this lesion, which shows little association with ambient blood pressure levels. However, this problem has yet to be solved.

Summary

A survey is reported of the courses of 84 patients who presented the syndrome of malignant hypertension and who have been under treatment with potent antihypertensive drugs.

Among these, 70 per cent survived 1 year of observation, 50 per cent 3 years, 33 per cent 5 years, and 26 per cent 6 years. These survival rates represent substantial therapeutic gains over survival rates in the untreated series of Keith, Wagener, and Barker.

The reported first-year survival rate is weighted by the untoward complication of hexamethonium pneumonitis, and current survival is greater than in the estimate presented.

Other causes of death are (1) rapidly or (2) delayed or slowly progressive renal failure and (3) complications of atherosclerosis. The first is usually associated with poor control of blood pressure. It seems merely an attenuation of the usual course of malignant hypertension. The syndrome of delayed or slowly progressive renal failure is associated with diffuse occlusive fibrous intimal hyperplasia of major renal arteries. Among the complications of atherosclerosis, cerebral hemorrhage was the most common and was associated with poor control of blood pressure level, while myocardial infarction, the next most common, was not. It may be that the coronary arteries, like the renal, are subject to progressive occlusive disease in some patients with treated malignant hypertension. It is not clear whether this process represents a continuation in vessels larger than arterioles, of a basic vascular disease or a delayed response on the part of the arteries to preexisting severe hypertension.

Survival is improved in patients who undertake treatment before malignant hypertension has caused extensive vascular damage. Patients who present themselves for treatment with evidences of severe renal damage generally do not survive for long periods. However, several such have maintained active lives for many months and years. Hence treatment should be withheld only in the most desperate circumstances.

Summario in Interlingua

Es reportate un studio del curso clinic de 84 patientes con le syndrome de hypertension maligne, tractate perdurativemente con potente drogas antihypertensive.

Ex le total de 84 patientes, 70 pro cento superviveva 1 anno de observation, 50 pro cento superviveva 3 annos, 33 pro cento superviveva 5 annos, e 25 pro cento superviveva 6

annos. Iste cifras de superviventia representa un considerabile avantiamento therapeutic in comparation con le cifras de superviventia in le serie de casos non tractate que esseva reportate per Keith, Wagener, e Barker.

Le supra-notate cifra de superviventia al fin del prime anno es deprimite per le adverse complication de pneumonitis a hexamethonium. Al tempore presente iste cifra esserea plus favorabile.

Causas de morte—altere que pneumonitis—es (1) insufficientia renal a progresso rapide, (2) insufficientia renal a progresso tardive o lente, e (3) complicationes de atherosclerosis. Le prime occurre usualmente in association con grados insufficiente de control del pression sanguinee. Illo pare esser simplemente un forma attenuate del curso usual de hypertension maligne. Le syndrome de insufficientia renal a progresso tardive o lente es associate con diffuse hyperplasia fibrose occlusive del intima de major arterias renal. Inter le complicationes de atherosclerosis, hemorrhagia cerebral esseva le plus commun e se trovava associate con inadequate control del pression de sanguine, durante que infarcimento myocardial—le proxime in le ordine de frequentia—occurreva sin ille association. Il es possibile que le arterias coronari (como le arterias renal) es susceptibile de disveloppar un progressive morbo occlusive in certe patientes con tractate hypertension maligne. Il non es clar si iste processo representa un continuation—in vasos plus grande que le arteriolas—de un morbo vascular fundamental o si illo representa un responsa tardive, del parte del arterias, al pre-existente grados sever de hypertension.

Le superviventia es meliorate in patientes qui recipe tractamento ante que le hypertension maligne ha causate extense damnos vascular. In general, patientes qui se presentia al tractamento con signos de sever grados de damno renal non supervive longemente. Tamen, in plus que un tal caso, le patiente ha mantenite un vita active durante multe menses e annos. Per consequente, le non-initiation del tractamento es justificate solmente sub le conditiones le plus desperate.

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ABSTRACTS

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METABOLIC EFFECTS ON CIRCULATION

Benda, L., Doneff, D., and Moser, K.: Influence of Cocarboxylase on Blood Pyruvic Acid in Cardiac Failure and Digitalis Intoxication. Ztschr. Kreislaufforsch. 47: 237 (Feb.), 1958.

In 15 patients with cardiac failure the blood pyruvic acid concentration was elevated, but became normal after treatment with digitalis. In 6 patients with digitalis intoxication the pyruvic acid was considerably elevated. In both groups of patients the pyruvic acid level could be decreased by intravenous injection of 200 mg. of cocarboxylase, and in 1 patient with digitalis intoxication bigeminal rhythm disappeared. Vitamin B_1 caused an inconstant decrease of pyruvic acid in patients with failure, but had no effect in those with digitalis intoxication.

LEPESCHKIN

Selye, H.: The Humoral Production of Cardiac Infarcts. Brit. M. J. 1: 599 (Mar. 15), 1958.

The author has produced infarct-like necrotic patches in the myocardium of rats treated concurrently with 2α-methyl-9α-chlorocortisol (Me-Cl-COL) and NaH_2PO_4. These rats invariably succumbed with the clinical manifestations of acute cardiac death and necropsy showed that histologically the myocardial lesions resembled true spontaneous cardiac infarcts in man. However, the experimental lesions differed from human infarcts in that there was a constant absence of any histologically demonstrable vascular occlusion. Hence, these lesions have been referred to as an "infarctoid cardiopathy" and to further distinguish these lesions from those infarct-like lesions due to other causes, the author applied the term "phosphate-steroid-cardiopathy." In order to determine whether a pre-existent coronary lesion would sensitize the cardiac muscle to this type of damage, albino rats were pretreated during 10 days with dihydrotachysterol (D. H. T.). This produced mild narrowing and calcification of the coronary arteries. After pretreatment all animals were given no further medication until they had recovered, as judged by their growth and clinical appearance. Then combined treatment with NaH_2PO_4 and 2α-methyl-9α-chlorocortisol (Me-Cl-COL) was started at a dosage level which in non-pretreated animals caused only occasional microscopic foci of myocardial necrosis, localized in certain areas of predilection. It was found that in the D.H.T.-pretreated rat this same NaH_2PO_4 plus Me-Cl-COL treatment produced extensive macroscopically visible patches of necrosis throughout the myocardium and, at the same time, evoked intense, proliferative, and eventually obstructive changes in all parts of the coronary tree. Further experiments will have to show whether there is any close relationship between this experimental disease and the spontaneous coronary infarcts of man. In addition, it remains to be seen whether the magnesium and potassium salts that proved to be so eminently effective in the prophylaxis of the phosphate-steroid-cardiopathy will also prevent those types of cardiac necroses that are associated with vascular obstructions.

KRAUSE

Hess, M. E., and Haugaard, N.: The Effect of Epinephrine and Aminophylline on the Phosphorylase Activity of Perfused Contracting Heart Muscle. J. Pharmacol. & Exper. Therap. 122: 169 (Feb.), 1958.

Isolated, contracting rat hearts were perfused with 0.01 per cent epinephrine and 0.05 or 0.1 per cent aminophylline and then analyzed for phosphorylase activity. The extracts showed a high degree of activity in the absence of added adenylic acid and an increase in activity on the addition of adenylic acid. The authors believe that such observations indicate that phosphorylases are present in heart muscle and that these are similar to the phosphorylase **a** and **b** that have been described to be present in skeletal muscle. Together with an increase in mechanical activity of the heart due to epinephrine or aminophylline administration there was a transformation of phosphorylase **b** to phosphorylase **a**. Epinephrine may act by activating the enzyme that catalyzes the formation of active phosphorylase. Aminophylline may work like epinephrine or through release of epinephrine bound in the heart cells.

RINZLER

PHARMACOLOGY

Maengwyn-Davies, G. D., and Walz, D. T.: Autonomic Drugs Modifying the Effects of N, N-Dibenzyl-Beta-Chlorethylamine (Dibenamine) on Dihydroxyphenylethanolamines. Arch. int. pharmacodyn. 113: 422 (Jan.), 1958.

In atropinized mongrel dogs under sodium pentobarbital anesthesia the blood pressure was recorded in the carotid artery. The influence of various drugs on the epinephrine reversal effect of dibenamine was studied by intravenous injection. Large doses of ephedrine given before or up to 1 hour after dibenamine changed the epinephrine reversal effect into a pressor effect and also potentiated the suppressed pressor response to norepinephrine. A ganglionic-blocking dose of hexamethonium given 30 minutes before dibenamine had a similar effect. Large doses of ephedrine diminished the blood pressure fall caused by Isuprel; hexamethonium instead enhanced this response and showed additive synergism with dibenamine. Although ganglionic blockade may contribute to the effect observed, this lasts longer than the blocking action of hexamethonium. The hypothesis is advanced that the effects observed result from an indirect influence of the drugs, mediated by the release of other substances.

CALABRESI

Karki, N. T.: Effect of Quinidine and Other Antimalarial Agents on the Uptake of Potassium Ions by Red Cells. Arch. int. pharmacodyn. 114: 243 (March), 1958.

Human blood is heparinized and stored for 3 to 5 days at about 2 to 4 C. The red cells lose potassium and gain sodium. When the blood is incubated at 37 C. with glucose, potassium is gained and sodium is lost by the red cells. It has been found that the uptake of potassium is diminished in the presence of quinidine, in linear proportion with the log of the concentration, between 12 and 200 μg. per ml. Other antimalarial substances, mepacrine, proguanil, and chloroquine, were found to have a similar action; pyrimethamine however has little or no effect; hence, the influence on potassium flux and the antimalarial effect appear to be independent. The implications of these observations on the mechanism of cardiac action of quinidine, in relation also to its antagonism to acetylcholine and to the extrusion of sodium, are briefly discussed.

CALABRESI

PHYSICAL SIGNS

Fleming, P. R.: The Mechanism of the Pulsus Bisferiens. Brit. Heart J. 19: 519 (Oct.), 1957.

Pressure pulses of 36 patients with aortic stenosis were recorded from the left ventricle and aorta before and after aortic valvotomy. These curves were superimposed to obtain the changing pressure gradient that was used as an approximation of the changing flow through the aortic valve. In 28 patients the aortic upstroke was prolonged, deformed by a notch and its peak delayed relative to that of the left ventricle. After successful aortic valvotomy, the peak was shortened and the anacrotic notch rose on the upstroke and became less prominent. On the other hand, if the aortic notch rose and its depth increased, clinical aortic regurgitation was present. In all instances, the anacrotic notch was present precisely at the moment of maximum flow. For this reason, the notch was regarded as a suction effect of a high velocity blood stream. When the notch was situated at the peak of the curve, pulsus biferiens was present, a sign of significant aortic regurgitation and mild stenosis and a contraindication to aortic valvotomy.

SOLOFF

Weissel, W.: The Diagnostic and Prognostic Significance of Presystolic Gallop Rhythm. Ztschr. Kreislaufforsch. 46: 829 (Nov.), 1957.

An audible atrial sound was found in 21 of 600 cardiac patients. As more than one half of these patients had heart failure, increased atrial

and ventricular diastolic pressure alone could not be responsible for the gallop. Myocardial fibrosis or aneurysmatic outward movement of the relatively thin cardiac apex in left ventricular hypertrophy was considered as the major contributing cause. In 16 patients the ratio of the amplitude of the atrial sound to that of the first heart sound in the medium frequency range (300 c.p.s.) was determined; the 4 patients who died within 12 months all had a ratio exceeding 0.75. Among the 21 patients with an audible atrial sound this was found to disappear within 3 years in only 1 patient, after treatment with radioactive iodine.

LEPESCHKIN

Auinger, W.: Differential Diagnosis of Accessory Heart Sounds in Mitral Stenosis. Ztschr. Kreislaufforsch. **46**: 865 (Nov.), 1957.

Of 162 patients with mitral stenosis, 18 showed 2 accessory heart sounds following the second sound and separated by intervals of 0.02 to 0.05 second. In 6 patients the first of these accessory sounds corresponded to the closure of the pulmonic valve, as it appeared later in inspiration and coincided with the incisura of the pulmonary artery pulse; the second accessory sound corresponded to the opening snap of the mitral valve, as it appeared later in the upright position, and was followed by the diastolic murmur. In 12 patients the first accessory sound was the opening snap while the second accessory sound was maximal over the apex and contained both high and low frequencies, the latter beginning later than the former. It varied with respiration, sometimes appearing only as an initial accentuation of the diastolic murmur. It coincided with the final diastolic downward movement of the pulmonary capillary pulse, and probably corresponded to the third heart sound.

LEPESCHKIN

PHYSIOLOGY

Eckstein, J. W., and Hamilton, W. K.: The Pressure-Volume Responses of Human Forearm Veins during Epinephrine and Norepinephrine Infusions. J. Clin. Invest. **36**: 1663 (Dec.), 1957.

This study was undertaken to determine whether venous constriction, induced by epinephrine or norepinephrine, is sufficient to move significant quantities of blood from the limbs. The experiments were performed on young healthy males by plethysmographic technics. During epinephrine infusion, forearm venous distensibility decreased although venous pressure increased. These responses were smaller when phentolamine (Regitine) was administered prior to a repetition of the epinephrine infusion. Norepinephrine caused a much greater rise in venous pressure and a slightly greater fall in venous distensibility than epinephrine in comparable doses. When the forearm was at the atrial level but the subject at rest in the supine position, only small inconsistent changes in forearm venous volume were noted after epinephrine. However, when the forearm was dependent, both drugs regularly caused large shifts of blood of comparable magnitude out of the forearm veins. Such venous shifts from dependent extremities in the upright position to the central venous reservoir may be important in augmenting the cardiac output at times of physiologic need.

WAIFE

Weissler, A. M., Leonard, J. J., and Warren, J. V.: Effects of Posture and Atropine on the Cardiac Output. J. Clin. Invest. **36**: 1656 (Dec.), 1957.

This was a study on the effects of drug-induced tachycardia in recumbent and upright subjects. Atropine was selected because of its cardioaccelerator effect, which in recumbency is associated with little or no alteration in stroke volume. Young normal male students served as subjects. The cardiac output was determined by a dye-dilution method in both a recumbent and tilted head-up position (60 degrees). In addition, the effects of an anti-gravity suit compression in tilted subjects was studied. The most striking observation was that with the subjects in a tilted position, atropine no longer elicited an increase in cardiac output. The failure of atropine in this regard can be in part reversed by the application of anti-gravity suit compression. Similar reductions in the stimulatory effects of atropine were observed during peripheral pooling of blood obtained by venous occlusive tourniquets. The data support the thesis that the central venous reservoir is an important determinant of cardiac responsiveness. It would appear that in the recumbent position more than adequate blood is available to meet the demands of sudden tachycardia. The atrial pressure is relatively high and cardiac filling occurs rapidly. However, on assuming the upright position the venous reservoir of the thorax is depleted, filling of the ventricle is slower, and the stroke volume falls although the heart rate is suddenly increased. The capacity of the heart to increase its output is more directly dependent upon the venous inflow. Under these circumstances, factors that increase the venous inflow, such as body compression, restore cardiac responsiveness.

WAIFE

Jeresson, B. J.: The Split Second Heart Sound and its Correlation to the Pulmonary Vascular Resistance. Cardiologia **32:** 155 (March), 1958.

The author studied the hemodynamics in relation to the second pulmonic sound in 12 normal persons, 4 patients with atrial and ventricular septal defects, and 1 patient with primary pulmonary hypertension. A good correlation was found between the degree of splitting of P_2 on the one hand and the pulmonary resistance and the duration of the protodiastolic phase of the right ventricle on the other; no correlation existed for the duration of right ventricular systole. In atrial septal defects the common finding of a right bundle-branch block may contribute to the separation of the 2 components of the second sound. In ventricular septal defects a right-to-left shunt may prolong left ventricular ejection and thus reduce the degree of splitting of the second sound. With normal intraventricular conduction and normal left ventricular output the split of the second pulmonic sound is an indirect measure of the pulmonary vascular resistance.

PICK

Mowlem, A., and Campbell, G. S.: The Acute Effects of Complete Heart Block on the Pulmonary Circulation. Surg., Gynec. & Obst. **106:** 333 (March), 1958.

Previous studies had shown that increased intracranial pressure in dogs resulted in bradycardia, reduced cardiac output, a moderate increase in mean pulmonary artery pressure, and a marked increase in mean pulmonary vein pressure with accompanying pulmonary edema. In order to evaluate the effects of the bradycardia itself, without direct cerebral influences on peripheral vascular resistance, complete heart block was produced in 17 animals by ligating the atrioventricular bundle. Subsequently there was a sustained average reduction in pulse rate to 48 per cent of control values, in cardiac output to 59 per cent, and in femoral artery pressure to 82 per cent; meanwhile, there was a transient twofold rise in left atrial pressure and a slight rise in pulmonary artery pressure. It was suspected that the absence of marked peripheral vasoconstriction prevented a shift of blood from the systemic to the pulmonary circuit, so that pulmonary capillary pressure did not rise sufficiently to produce pulmonary edema.

ROGERS

Lapal, E., and Bader, H.: On the Elastic Properties of the Aortic Reservoir. (Studies on Entire Human Aortas.) Ztschr. Kreislaufforsch. **47:** 66 (Jan.), 1958.

Registration of the postmortem aortic volume at different pressures indicated that the entire human aorta showed the same increase of the modulus of elasticity with age as the thoracic aorta. The increase of this modulus was much steeper than that of the volume elasticity modulus; the decreased elasticity of the aorta in advanced age was accordingly partly compensated by its increased diameter.

LEPESCHKIN

Fritts, H. W., Jr., Harris, P., Chidsey, C. A., III, Clauss, R. H., and Cournand, A.: Validation of a Method for Measuring the Output of the Right Ventricle in Man by Inscription of Dye-Dilution Curves from the Pulmonary Artery. J. Appl. Physiol. **11:** 362 (Nov.), 1957.

Dilution curves were simultaneously drawn from the pulmonary and brachial arteries in 9 subjects believed to have normal cardiorespiratory systems, and the calculated values of the cardiac output were compared to the value of output measured by the direct Fick method: The results indicate that both the pulmonary and brachial arterial flows agree with the Fick method within ± 15 per cent. The use of the pulmonary artery as a sampling site has several advantages: the segment of the cardiovascular system included between the injection and sampling points does not embrace a capillary bed which will allow for the use of diffusible indicators as saline to measure the right ventricular output; the problem of recirculation is minimized since, in most instances, the inscription of the primary curve is almost completed by the time recognizable recirculation appears; and the inscription of simultaneous pulmonary and brachial arterial curves should theoretically provide estimates of the individual outputs of the right and left ventricles. This last advantage can be used in the estimation of bronchial circulation since in patients in whom the blood enters the pulmonary circulation from the bronchial vessels by way of intrapulmonary anastomoses, the output of the left heart should exceed that of the right by the volume of the anastomotic flow.

RINZLER

Musshoff, K., Reindell, H., Klepzig, H., and Kirchhoff, H. W.: Heart Volume, Stroke Volume and Capacity to Perform Exercise. Cardiologia **31:** 359 (Nov.), 1957.

A statistical evaluation is presented of correlations between cardiodynamics and capacity to perform physical work studied in 57 normal young men, aged 22 to 25 years, and in 74 athletes, aged 18 to 32 years. The correlation was

based on the following determinations: cardiac volume calculated from roentgenograms, stroke and minute volume determined by cardiac catheterization and the Fick method, and the tolerance of exercise by simultaneous recording of oxygen consumption, pulse rate, and blood pressure during work on an ergometer. All determinations were made during a steady state.

In healthy subjects with a wide range of exercise tolerance, a direct correlation was found in the supine position between cardiac volume, maximal stroke volume, and exercise tolerance. On the other hand, a dependence of cardiac volume on body weight and surface was found only in persons with a normal range of ability to perform work and not in athletes. Exercise increased the stroke volume by 60 per cent. This increase was accomplished by ejection of residual blood, while diastolic heart size and filling pressure remained unchanged. This systolic volume reserve was proportional to the amount of residual blood.

PICK

Carlsten, A., Folkow, B., and Hamberger, C. A.: Cardiovascular Effects of Direct Vagal Stimulation in Man. Acta physiol. scandinav. **41**: 68 (Nov. 26), 1957.

The vagal control of the heart was studied in man during total neck dissection for cancer. The blood pressure, pulse rate, and pulse amplitude were recorded directly by means of a continuous intra-arterial blood pressure recording from an indwelling polyethylene catheter introduced into the brachial artery and connected to a strain-gage manometer. The electrocardiogram was recorded concomitantly for study of vagal effects on the pacemaker. The vagal nerve was blocked centrally to the site of the electric stimulation by a local injection of 1 per cent xylocaine solution into the nerve trunk. Stimuli were delivered by a Grass stimulator; rectangular, 5-millisecond pulses were used; the frequency ranged from 1 impulse every second to 20 impulses per second. Each stimulation period amounted to 10 seconds for every given frequency. The effector response, as measured by pulse rate, electrocardiogram, and blood pressure against the stimulation frequencies gave a hyperbolic curve. On stimulation of the left vagal nerve, the heart rate decreased maximally about 40 per cent; this effect was even greater on right vagal stimulation. A comparison between the heart rate before vagal xylocaine block and after direct stimulation showed that the tonic control of the heart was closely imitated by a stimulation rate around 2 to 4 impulses per second. The slowing of the heart rate was accompanied by a proportional fall in blood pressure, affecting both systolic and diastolic levels. The cardiovascular changes seen during operations by mechanical handling were believed to be predominantly of reflex origin and caused by activation of afferent vagal fibers, since the cardiovascular effects were eliminated if the vagal trunk was blocked by xylocaine central to the site of mechanical stimulation. No activation of the efferent fibers to the heart could be induced even by rough handling of the nerve trunk.

RINZLER

Berglund, E., Monroe, R. G., and Schreiner, G. E.: Myocardial Oxygen Consumption and Coronary Blood Flow during Potassium-Induced Cardiac Arrest and during Ventricular Fibrillation. Acta physiol. scandinav. **41**: 261 (Dec. 7), 1957.

The oxygen consumption of the heart in arrest was determined while the coronary vessels were perfused at a constant pressure from a donor dog. The values were compared with those obtained during ventricular fibrillation and cardiac work in the same dog. Cardiac arrest was induced by rapid injection of 10 to 20 ml. of a 5 per cent potassium citrate solution into the coronary artery tubing and was maintained for a desired period of time by a continuous slow infusion of the same solution. Ventricular fibrillation was induced by an electric shock of 60 cycles alternating current. Myocardial oxygen consumption, obtained as the product of coronary flow and coronary a-v oxygen difference, was reduced during arrest to values below 3.5 ml. per minute in 5 of 6 dogs studied. During fibrillation the oxygen consumption was 4 to 9 times as high as during arrest.

RINZLER

Cotten, M. D., and Maling, H. M.: Relationships Among Stroke Work, Contractile Force and Fiber Length During Changes in Ventricular Function. Am. J. Physiol. **189**: 580 (June) 1957.

There is a linear relationship between ventricular contractile force and ventricular stroke work during changes in either atrial or aortic pressures and during the changes produced by l-norepinephrine. There is also a direct relationship between the contractile force or stroke work and the end diastolic length of the segment of ventricular muscle between the 2 points of attachment of a heart-lever system employed to measure the contractile force. There was no consistent relationship between the stroke work or contractile force and the systemic output or stroke volume. The relative merits of measure-

ments of contractile force and stroke work in determining changes in ventricular contractility under a variety of conditions are discussed.

OPPENHEIMER

Angelakos, E. T., Laforet, E. G., and Hegnauer, A. H.: Ventricular Excitability and Refractoriness in the Hypothermic Dog. Am. J. Physiol. **189**: 591 (June), 1957.

The ventricular refractory period is greatly prolonged during progressive hypothermia. This effect is independent of changes in rate, since dogs with complete heart block at normal temperatures were not observed to have any great increase in refractory period. From 38 down to 23° C. heart temperature there is no change in ventricular diastolic excitability. Duration of relative and functional refractory periods is increased, which prolongs the rate of recovery of diastolic excitability and response latency. It is suggested that the slower rate of recovery of diastolic excitability may play a role in ventricular fibrillation during hypothermia.

OPPENHEIMER

Burn, J. H.: Ion Movement and Cardiac Fibrillation. Proc. Roy Soc. Med. **50**: 725 (Oct.), 1957.

Atrial fibrillation has been produced in the heart-lung preparation of the dog by applying brief stimulation to the atrium during the slow infusion of acetylcholine. Following this observation fibrillation has been produced in the isolated atria by stimulation in the presence of acetylcholine. Fibrillation occurs when the exchange of sodium and potassium ions reaches a certain value per unit of time.

Ventricular fibrillation has been studied in the isolated rabbit heart. When electric stimulation at a rate of about 600 per minute is applied to the ventricles until they fibrillate, the continuance of fibrillation after the stimulation has stopped has been shown to depend on various factors. Fibrillation is more likely to continue to lower the potassium concentration of the perfusing fluid, and to raise the calcium concentration. The effect of variation in the calcium concentration is, however, triphasic. Fibrillation is more likely to continue in the presence of dinitrophenol, and on the other hand, fibrillation is arrested in the presence of adenosine triphosphate. Fibrillation is attended by an increased loss of potassium ions from the ventricles.

MAXWELL

Scebat, L., Voridis, E., Renais, J., and Lenègre, J.: Study of the Mechanism of the Shunt in Interatrial, Interventricular and Aortico-pulmonary Communications. Arch. mal. coeur **50**: 518 (Sept.), 1957.

After hemodynamic study of 147 patients the conclusion was reached that while the direction and magnitude of the shunt depended on the pressure gradient across the opening, this gradient depended not only on the difference in pressure between the communicating cavities, but also on the direction and velocity of flow past the opening. This explained the observations that the magnitude and direction of the flow through the shunt may vary from instant to instant and may change in a direction opposite to that predicted from the difference in pressure between the communicating cavities under the influence of exercise or drugs. Under these conditions the flow in the shunt tends to change in a direction facilitating the conservation of a normal systemic output in relation to the oxygen needs of the organism; this regulatory mechanism becomes impaired with the appearance of pulmonary sclerosis.

LEPESCHKIN

Hegglin, R., and Wiesmann, W.: Behavior of Oxymetrically Determined Circulation Time. Cardiologia **31**: 109 (Fasc. 1), 1957.

The arm-ear and lung-ear circulation times were determined in 280 patients by the oxymetric method following injection of a dye indicator. In compensated cardiac patients both values deviated only slightly from the normal, whereas distinction of right and left ventricular failure by isolated prolongation of 1 or the other value was possible in some, but not in all instances. A definite relationship was found between heart size and circulation time and their comparison permitted a fair estimation of the degree of failure. On slight exercise the circulation time became shorter in normal individuals as well as in some cardiac patients demonstrating that an exercise test is not a reliable method for the detection of latent failure. Conspicuously short circulation times were encountered in thyrotoxicosis and in electrolyte disorders.

PICK

Bender, F., Hilgenberg, F., and Jungehülsing, G.: Continuously Registered Dye Dilution Curves in Acquired and Congenital Cardiac Malformations. Ztschr. Kreislaufforsch. **46**: 845 (Nov.), 1957.

After injection of 2 ml. of 0.5 per cent Evans blue into the pulmonary artery through a catheter filled with the dye the light absorption at the right ear was registered continuously. Compared to 11 patients with normal circulation, the beginning of the fall of the absorption curve in 15 patients with mitral disease was delayed in proportion to the severity of the disease. In the

presence of mitral regurgitation the ascent of the curve was prolonged much more than the descent. The same behavior was found in 11 patients with left-to-right shunt, who showed in addition a step in the descending branch and absence of the secondary elevation caused by re-circulation.

LEPESCHKIN

Nahas, G. G. and Cavert, H. M.: Cardiac Depressant Effects of CO_2 and Its Reversal. Am. J. Physiol. **190**: 483 (Sept.), 1957.

Acute myocardial failure is observed when the denervated heart-lung preparation is rendered acidotic by increasing abruptly above 5 per cent the carbon dioxide concentration in a respiratory gas mixture of carbon dioxide and oxygen. Evidences of this failing state include increased vena caval and left atrial pressures, decreased aortic pressure, diminished cardiac output against a constant resistance, and acute cardiac dilatation. After production of acidotic failure by administration of 15 per cent carbon dioxide for 3 to 5 minutes (arterial pH = 7.14 ± 0.05, output negligible), values for these variables (with the exception of pH) can be returned to control levels by injecting 4 micrograms per minute of epinephrine or norepinephrine. Furthermore, the signs of carbon dioxide failure do not appear if the epinephrine infusion is begun concomitant with high carbon dioxide ventilations. These results were interpreted as indicating that in the intact dog, cardiac tolerance to hypercapnia may be the result of a stimulation of the sympathoadrenal system, which counteracts the negative inotropic effect of carbon dioxide on the myocardium. Reversal of carbon dioxide-induced failure was also observed within 5 to 10 minutes after injection of 0.1 mg. of acetyl strophanthidin.

WENDKOS

Porjé, I. G., and Rudewald, B.: Physical Determination of the Stroke Volume. Cardiologia **31**: 389 (Nov.), 1957.

Physical determination of the stroke volume is defined by the authors as a calculation of the cardiac output per beat from physical data such as pressure curves, pulse wave velocity, and cross sectional areas of blood vessels. A new formula is proposed that has the great advantage of not containing values for pulse-wave velocity. The theoretical background and the mathematical derivation are presented in detail. The correctness of the formula was tested on a circulation model. Application of the new method in clinical cases revealed that its results compare favorably with the methods of Fick as well as of Hamilton.

PICK

PULMONARY DISEASES

Kuida, H., Dammin, G. J., Haynes, F. W., Rapaport, E., and Dexter, L.: Primary Pulmonary Hypertension. Am. J. Med. **23**: 166 (Aug.), 1957.

The clinical, hemodynamic, and pathologic features are presented of 4 patients with primary pulmonary hypertension who illustrate the difficulties in ruling out causes of secondary pulmonary hypertension. The important symptoms of pulmonary hypertension included exertional dyspnea, fatigue, cyanotic episodes, syncopal attacks, and angina-like chest pain. Electrocardiographic and roentgenologic evidence of right ventricular hypertrophy was found. Cardiac catheterization revealed elevated pulmonary artery pressures and calculated vascular resistance, diminished oxygen saturation, and cardiac minute outputs. The pathogenesis of the increased pulmonary vascular resistance remains obscure. Only 2 pathologic lesions were found common to all 4 cases, arteriosclerosis and arteriolosclerosis of the pulmonary arteries, both of which can be regarded as sequelae of pulmonic hypertension. The thesis is stressed that it is difficult if not impossible on clinical grounds alone to differentiate this lesion from a multitude of conditions in which pulmonary hypertension is secondary. Since a definitive diagnosis is only possible at necropsy, no effort should be spared to unearth a remediable lesion.

KURLAND

Austen, F. K., Carmichael, M. W., and Adams, R. D.: Neurologic Manifestations of Chronic Pulmonary Insufficiency. New England J. Med. **257**: 579 (Sept. 26), 1957.

Four cases of a clinical syndrome comprising symptoms and signs of pulmonary and cardiac failure, papilledema, headache, impairment of consciousness, and tremor and twitchings of the extremities are presented in detail. In each case the underlying cause was chronic pulmonary insufficiency, but the pulmonary disease differed in each. In all 4 patients congestive heart failure, left as well as right sided was present. The right-sided heart failure could be explained primarily on the basis of a decreased pulmonary vascular bed leading to pulmonary hypertension and heart failure. The pathogenesis of the left-sided heart failure was not clear but was thought to be due in large part to hypoxia and underlying coronary disease. In 2 patients headache was a prominent feature, occurring mainly at night and early in the morning. Papilledema indistinguishable from that associated with other causes of increased intracranial pressure, was present in 3 of the 4 patients. Some degree of

impairment of consciousness with drowsiness and inattentiveness progressing to actual stupor and coma was noted in each patient. In each of the 4 coarse twitching and tremor of the extremities were conspicuous findings. The twitching was identical with that often seen in hepatic coma. Electroencephalography revealed an abundance of activity in the slowed frequency ranges in all leads as the principal abnormality. These changes were reversible.

The neurologic disorders of this syndrome showed considerable variability from case to case in their relative prominence, time of appearance and rate of disappearance with treatment. The hypoxia and hypercapnia of pulmonary insufficiency were considered as the primary factors responsible for the neurologic syndrome with cardiac decompensation as a factor leading to further diminution of pulmonary sufficiency. The disorder of consciousness was attributed primarily to elevation of the carbon dioxide tension. The development of papilledema apparently required both hypoxia and hypercapnia. The cause of the movement disorder was obscure. In 3 of the patients the neurologic disturbance was completely reversed by a therapeutic program directed toward the restoration of cardiac and pulmonary compensation.

SAGALL

Galdston, M., and Geller, J.: Effects of Aminophylline and Diamox Alone and Together on Respiration and Acid-Base Balance and on Respiratory Response to Carbon Dioxide in Pulmonary Emphysema. Am. J. Med. **23**: 183 (Aug.), 1957.

Studies were performed to determine whether aminophylline and Diamox separately increased the sensitivity of the respiratory centers in patients with advanced emphysema and whether sustained reduction in the level of arterial pCO_2 and plasma $BHCO_3$ induced by Diamox enhanced the response to aminophylline. The sensitivity of response to 100 per cent O_2 and O_2-CO_2 mixtures was normal in the patients with moderate emphysema and decreased in those with severe emphysema. None exhibited a significant increase in sensitivity with the drugs although they lowered the threshold of response. Intravenous aminophylline caused a rise in minute ventilation and oxygen uptake in most patients. When administered 2 to 3 hours after a dose of Diamox it usually resulted in a greater ventilatory stimulation than when either drug was studied separately. This was accompanied by significant fall in arterial pCO_2 and a rise in alveolar pO_2. The fact that Diamox and aminophylline together increased the ventilatory response of patients with advanced emphysema to the arterial pCO_2 stimulus suggests that they may be effective in prevention and treatment of CO_2 retention and respiratory depression sometimes noted during the inhalation of oxygen-enriched air.

KURLAND

Van Epps, E. F.: The Roentgen Manifestations of Pulmonary Hypertension. Am. J. Roentgenol. **79**: 241 (Feb.), 1958.

Cardiac catheterization as a method of estimating pulmonary arterial pressures is expensive and not without some danger to the patient. There are limitations of the sphygmomanometer in peripheral arterial pressure determination and possibly the same limitations regarding variations of pressures with disease, emotion, posture, etc. may be anticipated in the catheterization pressures. The ravages of pulmonary hypertension can be assessed on roentgenograms of the chest regardless of whether the cause is primary or secondary. Estimation of the degree of pulmonary hypertension is reasonably accurate in pressure ranges of 0 to 30 mm. (normal), 30 to 70 mm. (moderate), and 70 mm. Hg or over (severe). Estimation of heart size, size of main pulmonary arteries, and their peripheral divisions, rate of attenuation of peripheral branches, loss of normal sharpness of outline of vessels, and evidence of neovascularity are the signs that evaluate pulmonary hypertension and all must be utilized. Routine evaluation of pulmonary vasculature is the easiest method of determining the pulmonary artery pressure. It is safe, inexpensive, and reasonably accurate.

KITCHELL

Charms, B. L., Brofman, B. L., Elder, J. C., and Kohn, P. M.: Unilateral Pulmonary Artery Occlusion in Man. J. Thoracic Surg. **35**: 316 (March), 1958.

The authors studied 28 patients with chronic lung disease using the method of temporary unilateral pulmonary artery occlusion. This technic, previously reported, is performed during cardiac catheterization and consists of occlusion of a pulmonary artery by a triple-lumen catheter with an inflatable cuff. When a main pulmonary artery branch is thus occluded there is necessarily an increased blood flow through the contralateral lung without an over-all increase in cardiac output. The results in patients with emphysema were variable. There was no correlation between the control main pulmonary artery pressure and the pressure following occlusion. However, in patients with granulomatous disease there was

a constant and marked increase in pressure following occlusion, and still further increase when exercise was added. In the patients with left ventricular heart disease and pulmonary disease there was no rise in pressure except in 1 patient where granulomatous lung disease was also present. One of the implications from these studies is that the elevated pulmonary artery pressure in emphysema is not necessarily due to arteriolar changes, but may be due to extravascular causes such as increased intrapleural pressure. The method may also be useful in evaluating the relative causes of disability in cases of combined left heart disease and pulmonary disease. In such instances, occlusion followed by increased pulmonary pressure would point to pulmonary vascular changes as the site of increased pulmonary resistance. On the other hand, if no rise followed occlusion it would implicate left atrial hypertension as the cause of high pulmonary resistance. Other applications of the method are discussed.

ENSELBERG

Rudolph, A. M., Paul, M. H., Sommer, L. S., and Nadas, A. S.: Effects of Tolazoline Hydrochloride (Priscoline) on Circulatory Dynamics of Patients with Pulmonary Hypertension. Am. Heart J. **55**: 424 (March), 1958.

The authors report a study of the effects of acute intravenous administration of tolazoline hydrochloride on the pulmonary and systemic arterial pressures, the pulmonary and systemic blood flow, and the pulmonary and systemic vascular resistance in 10 patients with pulmonary arterial hypertension. In 9 this was associated with congenital heart disease and 1 with no demonstrable cardiac lesion. The systemic vascular effects of tolazoline were manifested by flushing of the skin, rise in measured skin temperature, increase in digital blood flow, and decrease in calculated systemic vascular resistance. The pulmonary vascular resistance was not significantly affected in 9 patients and only moderately reduced in 1. Thus, the effectiveness of tolazoline in reducing pulmonary vascular resistance observed by other investigators was not corroborated in the present study. In this regard the authors consider the possibility that the elevated pulmonary vascular resistance associated with congenital heart disease may be due to organic changes, whereas in other diseases vascular spasm may play a significant role.

SAGALL

Schein, C. J., Rifkin, H., Hurwitt, E. S., and Lebendiger, A.: The Clinical and Surgical Aspects of Chronic Pulmonary Artery Thrombosis. Arch. Int. Med. **101**: 592 (March), 1958.

The authors review the literature and present 2 case reports. In almost all cases the predominant presenting symptom is severe and intractable dyspnea. Episodes of repeated pulmonary infarctions may be noted, often with a definite peripheral source for the pulmonary emboli. Frequently a history of substernal pain with radiation to the back and arms is obtained due to acute pulmonary hypertension. Mental confusion and recurrent syncopal attacks may result from decreasing cerebral blood flow. The typical physical findings are those of right ventricular failure, namely, engorged liver, increased peripheral venous pressure, and peripheral edema. The pulmonic second sound may be accentuated, but it can be normal as a reflection of the extremely low pressure in the pulmonary artery, which results from the extension of the thrombus. The electrocardiogram usually reveals right ventricular strain and the chest x-ray indicates enlargement of the right ventricle and dilatation of the pulmonary arteries with otherwise clear lungs. There is often a latent period that represents the accelerated phase of complete outflow tract obstruction. It is at this time that a pulmonary arterial thrombectomy should be attempted.

KRAUSE

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Bone, M., Braude, A. I., and Kleinman, H.: Complement-Fixing Antibody Response to M-Protein of Nephritogenic Streptococci in Glomerulonephritis. J. Lab. & Clin. Med. **50**: 705 (Nov.), 1957.

A complement fixation test has been devised for detecting type-specific antibodies to streptococcal M. protein. The results obtained by application of this test to sera from the Red Lake Indian children indicates that the Red Lake Streptococcus is a separate nephritogenic type, immunologically different from type 12, is widely distributed geographically, and evokes a prolonged immunologic response which provides evidence by complement fixation of past nephritogenic infection. The data obtained by application of this test to nephritics in Dallas suggest that nephritogenic streptococci contain a related antigenic substance other than the conventionally measured type-specific substance, which promotes a prolonged, but not indefinite, antibody response. The lack of reactivity noted when normal sera with high antistreptolysin titers were tested with the type 12 and Red Lake antigen supports the specificity of the test.

MAXWELL

Driscol, T. E., and Berne, R. M.: Role of Potassium in Regulation of Coronary Blood Flow. Proc. Soc. Exper. Biol. & Med. **96:** 505 (Nov.), 1957.

During increased metabolic activity of the myocardium, coronary vasodilatation occurs. Since potassium is released from actively contracting muscle, a study was undertaken in dogs to determine if this vasodilatation could be accounted for by the release of potassium. Intracoronary infusion of potassium chloride sufficient to elevate the coronary arterial plasma potassium concentration to levels of from 4.23 to 12.10 mEq. per L., produced increases in coronary blood flow that averaged 17.7 per cent. The changes in coronary blood flow produced by this means did not parallel the changes in plasma potassium concentration. When myocardial oxygen consumption and coronary blood flow were increased by infusion of 2, 4-dinitrophenol or epinephrine, asphyxia, or increased aortic pressure, potassium was not released from the myocardium. Thus, the authors concluded that it was improbable that potassium released from the active myocardium was responsible for the adjustment in coronary resistance which accompanied changes in metabolic activity of the myocardium.

KRAUSE

Cafruny, E. J.: Effects of Mercurial Diuretics on Renal Volume and Intrarenal Blood Flow. J. Pharmacol. & Exper. Therap. **121:** 225 (Oct.), 1957.

The effects of mercurial diuretics on the renal volume were studied by means of the use of trichloracetic acid solutions as diffusing media. These solutions precipitate protein and bleach tissue. A distinct line of demarcation between bleached and dark areas was discernible and marked the extent of acid penetration into the tissue. At various time intervals following the subcutaneous or intramuscular administration of mercurials the animals were sacrificed by decapitation, the kidneys removed and placed in the solution. Extent of the acid penetration into the tissue was determined by means of a calibrated reticule inserted into an ocular lens. The mercurials used were mercaptomerin, mersalyl and chlormerodrin. They were found to increase the rate of penetration of the trichloracetic acid solution through rat and dog kidney cortex, to increase the renal weight and to produce a marked cortical ischemia. Hyperemia of the medulla was seen in rat kidneys after mercurial injection but not in dogs. Depression of the renal flow or use of non-mercurial compounds failed to duplicate the increase in penetration. The conclusion is that increased penetration is the result of a decreased tissue density produced by an increase in renal volume. The administration of BAL corrected all of the above stated effects.

RINZLER

Brooks, R. V., McSwiney, R. R., Prunty, F. T. G., and Wood, F. J. Y.: Potassium Deficiency of Renal and Adrenal Origin. Am. J. Med. **23:** 391 (Sept.), 1957.

The clinical and detailed biochemical features of 3 patients with potassium deficiency are described. All 3 patients met the criterion for renal loss of potassium, continuous excretion of more than 20 mEq. per day when the plasma potassium was below normal. Plasma deficiency was also indicated by either potassium retention on balance studies or evidence of muscular paralysis and low muscle potassium. Case I is cited as an example of deranged control of electrolyte excretion by the hormone of the adrenal cortical carcinoma; the urine contained excess 17-ketosteroids and aldosterone and the tumor was found at operation and necropsy. Unusual aspects of careful balance studies are presented. Case II is an example of renal loss of potassium due to inability of the tubules to produce ammonium ion. Ample evidence of gross tubular dysfunction was present as well as data indicating the potassium loss was not primary. At postmortem examination, extensive renal changes were present and generalized miliary granulomatosis. Case III illustrates the difficulties of ascribing renal loss of potassium to defects of the renal tubule or to their hormonal control. Hypokaliemia and alkalosis, potassium deficiency, hypertension, and renal damage could reasonably be ascribed to either cause. At postmortem examination, a 20 mm. tumor of the adrenal cortex was noted and the kidney showed microscopic changes of malignant hypertension.

KURLAND

Hammond, J. D. S.: The Effect of Venesection upon Renal Function of Patients with Congestive Heart Failure. Am. J. M. Sc. **234:** 185 (Aug.), 1957.

Measurements of renal function were performed before and after venesection in 10 patients with congestive heart failure. Low renal plasma flow and glomerular filtration rates were demonstrated prior to venesection compared to control subjects. Venesection had no consistent effect upon renal circulation in the patients with heart failure. The determination of urinary sodium and chloride showed no significant changes in their excretion rates as a result of venesection. There was no correlation observed between the changes in renal circulation and electrolyte

excretion during and after venesection. The renal retention of salt was probably at the maximum level in cardiac patients. These findings were in marked contrast to the effect of venesection on normal subjects in whom salt excretion continues to decrease after renal circulation starts to return to its initial level. All patients experienced relief of dyspnea following the procedure, despite the absence of any effect upon renal circulation or the urinary excretion of salt. The clinical improvement may depend upon the decrease in pulmonary congestion and a reduction of the rigidity of the lungs known to exist in such patients.

SHERMAN

Papper, S., Saxon, L., Burg, M. B., Seifer, H. W., and Rosenbaum, J. D.: The Effect of Morphine Sulfate upon the Renal Excretion of Water and Solute in Man. J. Lab. & Clin. Med. **50**: 692 (Nov.), 1957.

Morphine sulfate was administered in therapeutic doses, subcutaneously and intravenously, on 22 occasions to 16 normal men undergoing water diuresis. In 17 of the 22 experiments, the administration of morphine was followed in 10 to 55 minutes by a decrease in urine flow of more than 2.0 ml. per minute. The decrease in flow was *unaccompanied* by a rise in urine osmolarity, but was associated with a decrease in endogenous creatinine clearance and the rate of total solute excretion. In 7 experiments, there was a late decrease in urine flow associated with a rise in urine osmolarity.

MAXWELL

RHEUMATIC FEVER

Shetlar, M. R., Payne, R. W., Strenge, H. B., and Faulkner, J. B.: Objective Evaluation of Patients with Rheumatic Diseases. III. Comparison of Serum Glycoprotein, Seromucoid, and C-Reactive Protein Determinations as Methods for the Evaluation of Patients with Rheumatic Fever. J. Pediat. **51**: 510 (Nov.), 1957.

The authors set out to find a reliable laboratory test enabling them to appraise the degree of rheumatic activity in an ill individual. Blood was obtained from rheumatic children studied on the Pediatric Wards of the Crippled Children's Hospital in Oklahoma City, who were classified by physical examination as either active or inactive at the time the blood samples were drawn. Serum glycoprotein, seromucoid, C-reactive protein and antistreptolysin-O determinations were done. Erythrocyte sedimentation rates (Wintrobe) were also measured. The results of the various determinations were then compared with the clinical evaluation. It was found that the C-reactive protein determination showed a normal value before the indvidual's activity had subsided. The antistreptolysin-O titer persisted elevated long after the individual's activity had subsided. The erythrocyte sedimentation rate was erratic in serial determinations. The glycoprotein and seromucoid determinations mirrored most closely the subsidence of rheumatic activity and the seromucoid determinations appeared to do this more closely than did the glycoprotein determinations. The authors believe that the seromucoid determination (when it is more refined and the technic for its determination simplified) may be the objective laboratory study that is sought for evaluation of rheumatic activity in patients ill with rheumatic diseases.

HARVEY

Harris, T. N., Friedman, S., and Tang, J.: Paradoxical Values of the Erythrocyte Sedimentation Rate in Rheumatic Fever: A Comparison Among Three Acute Phase Tests. Am. J. M. Sc. **234**: 259 (Sept.), 1957.

Nonspecific laboratory tests are employed frequently for the detection or measurement of the activity of rheumatic fever. These tests include the erythrocyte sedimentation rate (ESR), serum mucoprotein (MPT) and serum C-reactive protein (CRP), which probably reflect destruction of tissue due to inflammation and other factors. The 3 acute phase tests were conducted in a series of patients with acute rheumatic fever in situations where the ESR may not provide a valid index of the inflammatory process. In 7 patients with acute carditis associated with heart failure, the ESR determination yielded values below 12 mm. per hour; when heart failure improved the ESR increased. Ultimately, in convalescence, the ESR returned to normal. The CRP values were apparently unaffected by the presence of heart failure. Each of teh 3 acute-phase tests was sharply reduced by ACTH and cortisone at therapeutic dose levels; the MPT levels were less affected than the other 2. In 2 patients with sickling trait the values of ESR were low but were apparently increased over the normal levels for these patients. The CRP and MPT were found to be elevated and did not show an increased rate of return to normal levels, indicating that they may be useful as indicators of rheumatic activity in patients with sickling trait. There were 11 children with persistent elevations of ESR for several months after disappearance of clinical evidence of rheumatic activity in whom the CRP and MPT were found to be within normal range.

SHUMAN

Massell, B. F., Fyler, D. C., and Roy, S. B.: The Clinical Picture of Rheumatic Fever. Diagnosis, Immediate Prognosis, Course, and Therapeutic Implications. Am. J. Cardiol. 1: 436 (April), 1958.

The major evidences of the initial attack of rheumatic fever are described as observed in 490 patients under age 17 during the years 1941 to 1951 in Boston. The findings of greatest diagnostic importance with respective incidences were: significant murmurs, 53 per cent; joint pain, 90 per cent; fever, 89 per cent; elevated erythrocyte sedimentation rate, 92 per cent; antistreptolysin-O titer of over 400. units, 82 per cent; prolonged P-R interval, 25 per cent; pericardial friction rub, 6 per cent; subcutaneous nodules, 12 per cent; and erythema marginatum, 11 per cent. Significant murmurs developed early in the course of the disease, being noted in 80 per cent of the patients with murmurs by the eighth day of illness. Prolongation of the P-R interval was almost as common among the group having no important murmur. Of the patients treated with symptomatic measures plus prophylactic penicillin, rheumatic activity had subsided after 6 weeks in 26 per cent and after 12 weeks in 78 per cent. Therapy with a potent anti-inflammatory agent is advocated for the individuals presenting carditis, since this feature is of prime significance in determining prognosis. Eight per cent of patients developed congestive heart failure and one fourth of these died.

ROGERS

ROENTGENOLOGY

Beall, A. C., Jr., Crawford, E. S., Couves, C. M., DeBakey, M. E., and Moyer, J. H.: Complications of Aortography. Factors Influencing Renal Function Following Aortography with 70 Per Cent Urokon. Surgery 43: 364 (March), 1958.

The most common significant complication of aortography is renal damage, which constitutes the major risk of the procedure. Studies were conducted on dogs and on patients to determine those factors related to the development of functional renal changes following this procedure. The pattern of functional alteration and degree of renal damage were quantitatively studied through determinations of glomerular filtration rate, renal blood flow, and water and electrolyte exeretion. Three variables with respect to the administration of Urokon were investigated: (1) dosage used, (2) site of injection, and (3) alteration in hemodynamics in the region of the kidneys. The immediate renal hemodynamic response, confirmed by both experimental and clinical observations, following the intra-arterial injection of Urokon is vasospasm of the injected vessel and its tributaries. This response may persist for as long as 2 hours following aortography. Anatomic and functional damage invariably resulted when the contrast material was injected directly into the renal arteries. Neither arteriosclerotic occlusion of the aorta below the renal arteries in man, nor experimental occlusion of the aorta below the renal arteries in dogs appeared to influence the production of renal damage following aortography. The rapidity with which the acute renal hemodynamic response returned to normal appeared to be related primarily to the amount of contrast material reaching the kidneys. These studies, as well as clinical experience in 200 patients, would appear to indicate that renal damage will not result from the use of 30 ml. or less of 70 per cent Urokon if direct renal artery injection is avoided.

BROTHERS

Biörck, G., Vendsalu, A., and Johansson, S.: Studies in Functional Heart Disease. II. The Roentgenological Heart Volume. Acta med. scandinav. **159:** 443 (Dec. 28), 1957.

This study was undertaken to test the validity of the observation that small hearts are commonly seen in patients with functional heart disease. Heart volume determinations were made roentgenologically in 213 patients with functional heart disorders and in a control group of 688 patients whose chest x-rays had been interpreted as showing normal hearts. The heart volume was determined by a modification of the Rohrer-Kahlstorf formula. In the functional heart disease group of 213 patients, 84 (39.4 per cent) had small hearts. Of these 84 patients, 25 were men (29.8 per cent) and 59 (70.2 per cent) were women. Among 688 patients with a previous x-ray diagnosis of normal heart, 159 (23.1 per cent) were found to be small. In this group, 59 (37.1 per cent) were men and 100 (62.9 per cent) were women. When comparisons were made between the 2 groups of patients in various age brackets for men and women, it was found that the differences were significant only in the group of women 30 to 39 years old and probably significant in the group of women 40 to 49 years of age. The authors conclude that this study corroborates earlier observations of a high incidence of small hearts in patients considered to suffer from functional heart disease. Small hearts, however, are found in a variety of morbid conditions as well as in healthy people and the finding of a small heart in functional heart disease has no pathologic significance per se in the individual

case. Nevertheless, a small heart seems to be one of the few objective characteristics that is rather frequent in this group of cardiac disorders and should, therefore, be subjected to further and more detailed studies.

BROTHERS

Schobinger, R., Blackman, G., and Lin, R. K.: Operative Intestinal Arteriography. Acta radiol. **48**: 330 (Nov.), 1957.

Angiography of the vascular channels of the intestinal tract is accomplished by the injection of contrast medium into the principal artery of the area under study during operative exposure of the vessel. Preparations for the study include testing for possible idiosynerasy to the contrast medium and local anesthetic agent and a preliminary film to assure proper positioning of the patient. Hypaque and procaine hydrochloride are injected through a catheter introduced into the appropriate artery through a 17-gage spinal needle. The operative arteriography is innocuous as shown by the absence of immediate or late ill effects during the period of direct observation of the bowel or during the uneventful postoperative course of the patient. The normal bowel demonstrates a uniform vascular pattern in contradistinction to the changes observed radiographically in the presence of lesions such as adenocarcinoma or polyps. The vascularity of these lesions produces areas of increased radiopacity; the cellular composition of the defect is not reflected in the arteriograms. Technical factors may interfere such as difficulty in controlling intestinal peristalsis and respiration; however, satisfactory roentgenograms were obtained in the majority of instances. This method permits an adequate evaluation of the collateral blood supply of large segments of the intestine.

SHUMAN

Nylin, G.: The Clinical Applicability of Roentgenological Heart Volume. Determination with Special Reference to the Residual Blood. Acta cardiol. **12**: 588 (Fasc. 6), 1957.

Because the heart is a tridimensional body, the true heart size cannot be determined by roentgenologic measurements in the frontal plane. The author presents his method and formulas derived from measurements in teleroentgenograms in 2 planes. The total heart volumes calculated by this method showed a good correlation with the body surface. Its upper normal limits were 500 ml. per $M.^2$ in men and 450 ml. per $M.^2$ in women. Physiologic and pathologic alterations of these values are dependent on changes in the amount of residual blood in the heart. Objective information concerning such changes can be obtained with the help of intravenous injection of tagged radioactive erythrocytes, determination of their circulation time, and mixing with the residual blood of the heart. Mathematical evaluation of such dilution curves permits a calculation of the blood content of the heart and lungs—the "thoracic pool"—under normal and pathologic conditions. Data are presented demonstrating the application of the method to normal individuals as well as in cardiac patients. Whereas in normal hearts the "thoracic pool" is low and rather constant, it would appear that the first sign of impaired cardiac efficiency is cardiac dilatation in association with increased residual blood in the heart. Since successful medical or surgical treatment leads to reduction of abnormal heart volume, the method has practical value in the assessment of therapeutic procedures.

PICK

Lyons, H. A.: The Use of Angiocardiography as an Aid in the Diagnosis of Pulmonary Disease. J. A. M. A. **165**: 1939 (Dec. 14), 1957.

The author has carried out angiocardiography with 70 per cent sodium acetrizoate as the contrast medium in more than 600 patients with pulmonary disease without a single fatality. This examination is a very important complementary procedure to other pulmonary study methods and may be the only examination which shows the true nature of the abnormality. Seven cases are reported illustrating its usefulness in distinguishing between vascular and nonvascular lesions of the lung and distinguishing between the need for surgical or medical treatment. The procedure is often essential for the diagnosis of pulmonary arteriovenous fistula and quite helpful in evaluating thoracoplasties. It should be more frequently employed in the study of pulmonary disease.

KITCHELL

Soloff, L. A., Zatuchni, J., Mark, G. E., Jr., and Stauffer, H. M.: The Size of the Pulmonary Artery in Rheumatic Heart Disease with Isolated Mitral Stenosis and Its Significance. Am. J. M. Sc. **234**: 313 (Sept.), 1957.

The combined technic of cardiac catheterization and sequential biplane stereoscopic venous angiocardiography was employed in 25 patients with rheumatic heart disease and isolated mitral stenosis to determine the diameter of the pulmonary artery and its relationship to that of the aorta, to age, and to various parameters of cardiac structure and function. The aortic diameters were normal and usually less than that of the pulmonary artery. The volume of the left

atrium or heart size could not be correlated with the pulmonary artery diameter. A fair correlation was found between the pulmonary artery diameter and the mean pulmonary wedge pressure. The correlation was better with the difference in mean pulmonary artery pressure alone. In 1 patients, a good correlation was observed between the diameter of the pulmonary artery and total pulmonary resistance; the correlation with pulmonary vascular resistance was of questionable significance. The findings indicate that direct measurement of the diameter of the pulmonary artery from contrast roentgenologic study cannot predict the degree of elevation of pulmonary artery pressure because the individual variation is so great that for any given diameter the mean pulmonary artery pressure varies widely.

SHUMAN

SURGERY AND CARDIOVASCULAR DISEASE

Ellis, F. H., Jr., Kirklin, J. W., and Bruwer, A. J.: Surgical Experiences in the Treatment of Aneurysms of the Thoracic Aorta. Surg., Gynec. & Obst. **106:** 179 (Feb.), 1958.

Twenty patients underwent thoracotomy for thoracic aortic aneurysms that were subjectively troublesome or dangerous in size. Two thirds of the patients were older than 50 years, and most of the lesions were arteriosclerotic (7) or syphilitic (5). Five aneurysms involving the aortic arch were technically unsuitable for resection. The remaining 15 were resected, 12 receiving homografts and 2 plastic grafts. Hypothermia of 26 to 30 C. was employed to protect vital tissues; and in only 1 patient, whose aorta was occluded for 90 minutes, was there obvious spinal cord dysfunction postoperatively. Ten of the 15 patients recovered and remained in good health for over a year. Most of the 5 deaths were due to hemorrhage. Considering the poor prognosis of these patients if untreated, the high operative mortality rate is not prohibitive, and it should decrease as surgical experience is gained in this new field.

ROGERS

Williams, J. A., Littmann, D., and Warren, R.: Experiences with the Surgical Treatment of Mitral Stenosis. New England J. Med. **258:** 623 (March 27), 1958.

The experiences with the surgical treatment of 52 patients with mitral stenosis are reported. The unusual features of this series were the predominantly male distribution (51 males and 1 female), the frequency of hemoptysis prior to surgery (70 per cent) and the high incidence of calcific involvement of the mitral-valve leaflets (83 per cent). In 47 patients the preoperative diagnosis of mitral stenosis was substantiated at operation. Although 5 patients had physical findings consistent with mitral stenosis, at operation it was found that 3 had pure mitral regurgitation and 2 had nonvalvular heart disease. In 15 patients with significant mitral stenosis and without atrial fibrillation a heretofore undescribed T-wave, termed "T-mitrale," was observed. This pattern was seen most clearly in leads V_3 or V_4 and consisted of an unusually tall and sharp T wave following a wide P wave. It was concluded that this "T-mitrale" might be the earliest electrocardiographically detectable indication of right ventricular hypertrophy. In the 47 patients in whom commissurotomy was performed, there were 6 operative deaths—3 due to embolization and 3 to cardiac failure. Two patients later succumbed to recurrent rheumatic carditis. Of the remaining 39, follow-up studies (during an average period of 29 months since surgery) indicated that 35 were benefited by the operation. Improved functional status postoperatively was usually, but not always, accompanied by a reduction in pulmonary hypertension. The possible mechanisms underlying the hemoptysis in these patients is discussed. The limitations of catheterization of the right side of the heart in the differential diagnosis of pulmonary hypertension is also discussed.

SAGALL

Tananbaum, H. L., Braunwald, E., and Morrow, A. G.: Determination of Cardiac Output and Pressure Gradients at Operation. A Technic for the Immediate Assessment of the Results of Operations for Stenotic Valvular Disease. New England J. Med. **258:** 527 (March 13), 1958.

The authors describe a technic used in 24 patients for measuring the cardiac output and valve-pressure gradients during the course of operations for mitral, aortic, tricuspid, and pulmonic stenosis. The necessity of determining flow as well as pressure differences in the immediate assessment of these procedures is emphasized, particularly when general hypothermia is employed. Selected clinical examples illustrating the application of the method are presented.

SAGALL

Cohen, M. G., and Pastor, B.H.: Delayed Cardiac Arrhythmias Following Non-Cardiac Thoracic Surgery. Dis. Chest **32:** 435 (Oct.), 1957.

Of 92 patients, 15 (16.3 per cent) developed postoperative arrhythmias. These occurred in

the first 2 days postoperatively in 5 patients, and between the third and fourteenth day in 10 patients. The incidence was greatest after pneumonectomy (32.5 per cent) and after mediastinal exploration and biopsy for neoplastic disease (30 per cent). All the common atrial arrhythmias, including atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, and multiple atrial premature contractions were observed. The majority responded to conventional therapy. The authors thought that the probable cause of delayed cardiac arrhythmias was chronic vagal stimulation and anoxia in an age group where coronary sclerosis was prevalent.

MAXWELL

Burack, B., Schwedel, J. B., and Young, D.: The Role of Digitalis in Mitral Valvuloplasty. Am. Heart J. **54**: 863 (Dec.), 1957.

Observation on the digitalis requirements of 50 patients with mitral valvuloplasty showed a need for increased digitalis in the preoperative period. Atrial fibrillation, often associated with congestive heart failure, was noted postoperatively in all patients with regular sinus rhythm who had received either no digitalis or inadequate amounts of digitalis during the preoperative period. Inadequately digitalized patients with preoperative atrial fibrillation developed rapid ventricular rates and congestive heart failure under anesthesia or during the postoperative period. On this basis it is recommended that in order to afford the myocardium greatest protection against arrhythmias and congestive heart failure all patients who are to undergo mitral valve surgery have prolonged and full digitalization regardless of the cardiac rhythm or lack of evidence of congestive failure. The patient's ventricular response to exercise during the preoperative preparatory period is regarded as an important criterion for adequate digitalization.

SAGALL

Duchesne, E. R., Abbott, O. A., Roberts, A. E., and Salomone, F. P.: A Comparison of Six Procedures Designed to Increase the Blood-Supply of the Myocardium. Brit. J. Surg. **190**: 194 (Sept.), 1957.

Two-hundred six operations were performed on 113 dogs in an attempt to determine the degree of protection afforded the myocardium following ligation of the anterior descending coronary artery. The procedures evaluated were the Beck I, Beck II, Fauteux, Thompson, Vineberg, and "combined" (Beck I with denervation of the left main coronary plexus). The authors believe that the Beck I presented the most over-all satisfactory immediate and long-term results.

MAXWELL

Matejicek, E., Takac, M., and Stubnova, G.: The Electrocardiogram of the Transplanted Heart. Cardiologia **31**: 589 (Dec.), 1957.

Successful heart transplantation with survival up to 5 days was accomplished in 24 dogs. The donor's heart was grafted into the chest cavity of the recipient and connected in a proper way with the recipient's circulation. Electrocardiograms are shown recorded during various stages of the procedure and on successive days after closure of the chest. The tracings reveal electric activity of both the donor's and recipient's hearts, the action being independent. Low amplitude of the action potentials of the transplanted heart is attributable to a number of factors such as an altered projection of the potentials, changes in the hemodynamic conditions, biochemical alterations in the myocardium due to disturbances of blood supply, and to immunologic reactions of the myocardium.

PICK

UNCOMMON FORMS OF HEART DISEASE

Robertson, R.: Primary Cardiac Tumours. Surgical Treatment. Am. J. Surg. **94**: 183 (Aug.), 1957.

Five patients with primary cardiac tumors treated surgically are reported. In 4 patients, the tumors arose from the pericardium. A 2-year-old child with teratoma of the pericardium and a 47-year-old woman with a mesothelial sarcoma of the pericardium did not survive the operative procedure. A 34-year-old woman with cylindroma (?) of the pericardium remained well for 5 years following excision of the tumor but died of local recurrence of the tumor. A lymphangioma of the pericardium was successfully removed from a 10-year-old boy. He had had symptoms since the age of 1 month and had been diagnosed as having congenital heart disease. The fifth patient, a 39-year-old woman, had myxoma of the left atrium successfully removed, utilizing the technic of hypothermia. The diagnosis had been made 16 months earlier when the patient was operated upon for what was thought to be mitral stenosis. In removing tumors from the surface of the heart care must be exercised to prevent injury to the coronary arteries and the aorta to which they may be firmly attached. These difficulties occurred in 2 of the patients presented and in the 2-year-old child with the

teratoma, involvement of the right coronary artery in the tumor undoubtedly contributed to the fatal outcome. Slides prepared from the myxoma and stained with colloidal iron were strongly positive for acid mucopolysaccharides. The author believes this staining method to be of value in differentiating an organizing atrial thrombus and myxoma, for thrombi stained in similar fashion failed to show comparable accumulations of acid mucopolysaccharides.

BROTHERS

Cary, F. H., Hurst, J. W., and Arentzen, W. R.: Acquired Interventricular Septal Defect Secondary to Trauma. Report of Four Cases. New England J. Med. **258:** 356 (Feb. 20), 1958.

Four new cases of traumatic interventricular septal defect are reported. In 3 patients the defect resulted from a penetrating chest injury. These patients are still alive and the defects were demonstrated by cardiac catheterization. The fourth patient suffered a rupture of the interventricular septum and severe myocardial contusion as a result of a crushing injury to the chest in an automobile accident. He died about 52 hours after the accident and the cardiac lesions were demonstrated at postmortem examination. His case also illustrates the frequent absence of external evidence of trauma or rib fractures in patients who sustain heart damage as the result of nonpenetrating chest injuries.

SAGALL

Tregubova, K. L., Levin, G. L., and Ado, M. A.: Primary Amyloidosis with Lesions Predominating in the Heart and the Tongue. Klinich. Med. 36/2: 101, 1958.

A 71-year-old man with hypertension developed enlargement of the tongue and congestive failure refractory to digitalis; the electrocardiogram was suggestive of an anterior myocardial infarction scar. Autopsy disclosed patent coronary arteries but extensive deposits of amyloid with atrophy of adjacent muscle fibers, predominantly in the ventricular septum and anterior papillary muscle, and in the tongue. It was concluded that refractory cardiac failure with macroglossia should suggest the diagnosis of primary amyloidosis.

LEPESCHKIN

Buhr, G.: On Cardiac Dynamics in Myxedema. Ztschr. Kreislaufforsch. **46:** 859 (Nov.), 1957.

In a patient with typical myxedema with marked cardiac dilatation the heart output was considerably reduced, the calculated elastic peripheral resistance and pulse-wave velocity were low while the tension period of the left ventricle was prolonged. That these changes were not due to myocardial failure was shown by the fact that they persisted after digitalis and that the intracardiac pressures were normal. All values returned to normal after thyroid treatment, and the isoelectric T waves also became normal.

LEPESCHKIN

Seide, M. J.: Heart Failure Due to Extreme Obesity: Report of a Case, with Autopsy Findings. New England J. Med. **257:** 1227 (Dec. 19), 1957.

The case of a 43-year-old massively, obese man with somnolence, lethargy, and failure of the right ventricle is presented. Laboratory and clinical studies revealed arterial hypoxia, hypercapnia, secondary polycythemia, right axis deviation, decreased vital capacity, and decreased maximum breathing capacity. Despite treatment progressive and irreversible respiratory-center narcosis developed. At autopsy the only significant findings were hypertrophy of the right ventricle and right atrium. In the pathogenesis of this syndrome obesity is considered to cause diminished excursion of the thorax and diaphragm thereby leading to alveolar hypotension and resultant pulmonary hypertension with eventual right ventricular heart failure. The arterial hypercapnia (and also the associated hypoxia to some degree) lead to symptoms of carbon dioxide narcosis, somnolence, mental confusion, weakness, lassitude, irritability, tremor or twitching, warm flushed skin, sweating, tachycardia, hypotension, and sensitivity to small changes in acidosis. In treatment ammonium chloride, acetazolamide, other acidifying agents, narcotics and sedatives should be avoided and oxygen given only with caution, since each of these agents can increase narcosis and may cause death.

SAGALL

Teare, D.: Asymmetrical Hypertrophy of the Heart in Young Adults. Brit. Heart J. **20:** 1 (Jan.), 1958.

The author describes an unusual asymmetric hypertrophy of the myocardium in 8 young persons who died suddenly and in 1 who died after mitral valvotomy. This last one had a localized hypertrophy of the interventricular septum that distorted the mitral valve and gave rise to signs of mitral stenosis which led to valvotomy and death. Microscopically, this lesion is characterized by bizarre arrangement of bundles of muscle fibers running in diverse directions and separated by connective tissue and clefts. The connective tissue breaks up and interrupts the muscle bundles. The clefts are lined with endothelium that

covers sparse elastic tissue similar to the structure of the normal endocardium. Patients usually have no symptoms before sudden death or may have palpitation due primarily to atrial fibrillation, fits, or blackouts. One of the 8, a woman, had a brother who subsequently died of the same lesion and has a living sister whose symptoms are identical with those of the sister who died.

SOLOFF

ERRATUM

RUBIN, A. L., LUBASH, G. D., COHEN, B. D., BRAILOVSKY, D., BRAVEMAN, W. S., AND LUCKEY, E. H.: Electrocardiographic changes during hemodialysis with the artificial kidney. Circulation: **18:** 227-234 (August), 1958.

On page 229, figure 3 was inadvertently omitted. The arrangement of figures 2 and 3, with legends, should have appeared as shown to the right.

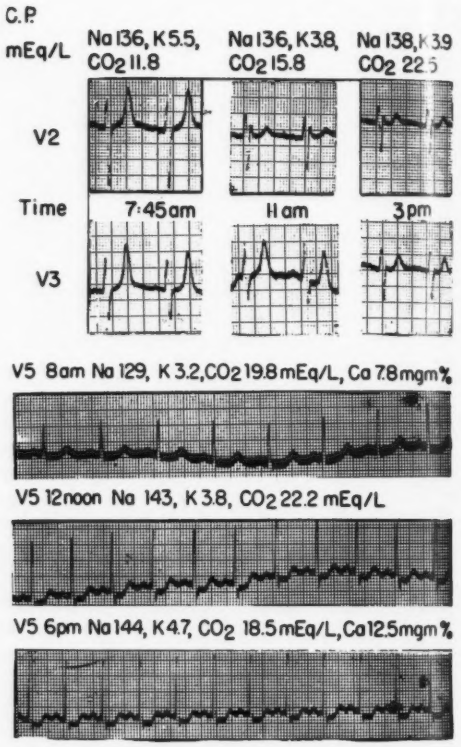
C.P.
mEq/L
Na 136, K 5.5, CO2 11.8
Na 136, K 3.8, CO2 15.8
Na 138, K 3.9 CO2 22.5
V2
Time
7:45am
11am
3pm
V3
V5 8am Na 129, K 3.2, CO2 19.8 mEq/L, Ca 7.8 mgm%
V5 12noon Na 143, K 3.8, CO2 22.2 mEq/L
V5 6pm Na 144, K 4.7, CO2 18.5 mEq/L, Ca 12.5 mgm%

FIG. 2 *Top.* Note change in peaked T waves with correction of acidosis and slight hyperpotassemia during dialysis.

FIG. 3 *Bottom.* Note appearance of ST-wave depression as hypocalcemia was corrected during dialysis. The patient had received digitalis. The increase in ventricular rate does not account for the degree of change.

AMERICAN HEART ASSOCIATION, INC.

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AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS

Approximately 3,000 physicians, research scientists and lay leaders from all parts of the country are expected to attend the Association's 34th Annual Meeting and 31st Scientific Sessions in San Francisco, October 24-28. Headquarters for those attending the Scientific Sessions, to be held in the Civic Auditorium, Friday, October 24 through Sunday, October 26, will be the Hotel Fairmont.

A total of 90 original scientific papers have been selected for presentation at the Scientific Sessions from over 360 submitted for consideration by the Committee on Scientific Sessions Program. Approximately 30 additional papers will be given by invited speakers. Titles and authors of all papers to be presented are listed on pages 679-685. Information about medical films, scientific and industrial exhibits, and other features of the scientific program will be found on pages 805-813.

Highlights of the Scientific Sessions this year include an all-day Session for Clinicians and joint participation in the program by the American Society for the Study of Arteriosclerosis and the Microcirculatory Conference.

The Sessions for Clinicians, sponsored by the American Heart Association's Council on Clinical Cardiology, are scheduled for Friday, October 24. Included are symposia on "Congenital Heart Disease," "Treatment of Intravascular Clotting," and "Peripheral Arterial Insufficiency." Other timely subjects are "Clinical Evaluation of Chlorothiazide," "Traumatic Heart Disease," and "The 'Tough Case' of Bacterial Endocarditis." A panel discussion will be held on "What's New in Arrhythmias." The Scientific Sessions for Clinicians have been accepted for credit by the American Academy of General Practice.

NOVEMBER 1 IS DEADLINE FOR AHA GRANT-IN-AID APPLICATIONS

Applications for Heart Association grants-in-aid for the fiscal year beginning July 1, 1959 must be received by the Assistant Medical Director for Research at the AHA National Office, 44 East 23rd Street, New York 10, N. Y., not later than November 1, 1958. All applications must be made on forms available from the AHA. Grants are made to non-profit institutions in direct support of a particular investigator, for a specific program of research under his direction. Grants are awarded in support of research in the cardiovascular field or basic sciences for periods of one to five years.

The program to be presented jointly by the American Society for the Study of Arteriosclerosis and the American Heart Association opens on Friday morning, October 24, with a symposium on "Genetic Factors in Cardiovascular Disease." A second joint session, on Arteriosclerosis, will be held Saturday afternoon.

The joint session of the Association's Council on Circulation and the Microcirculatory Conference, to be held Friday afternoon, October 24, includes symposia on "Vascular Thrombosis," "Cerebral Circulation," and "Vascular Reactivity."

Events of special interest during the Scientific Sessions and Annual Meeting are as follows:

Friday, October 24

Morning: Joint ASSA-AHA Session on Genetics; Concurrent Session for Clinicians;

Scientific Sessions sponsored by the Council on Circulation and the Council on Cardiovascular Surgery.

Afternoon: Scientific Session of Council on Rheumatic Fever and Congenital Heart Disease.

Evening: Scientific Session on "Instrumental Study of the Heart and Circulation."

Saturday, October 25

Morning: General Session on "Applied Cardiovascular Research"; Lewis A. Conner Memorial Lecture by Dr. John H. Gibbon, Jr., Philadelphia; George E. Brown Memorial Lecture by Dr. Lewis Thomas, New York; Presentation of the Albert Lasker Award of the AHA for cardiovascular research.

Afternoon: Panels on Arteriosclerosis to be presented jointly with the American Society for the Study of Arteriosclerosis.

Sunday, October 26

Morning: Simultaneous Scientific Sessions conducted by the Councils on Clinical Cardiology, High Blood Pressure Research, and Basic Science.

Afternoon: Special program arranged by Council on Community Service and Education, "Rewards of Research," which will be of interest to physicians as well as laymen; Session on Rheumatic Fever Secondary Prevention Programs sponsored jointly by the Councils on Rheumatic Fever and Congenital Heart Disease, and Community Service and Education.

Evening: AHA Annual Dinner at Fairmont Hotel; presentation of Gold Heart Awards.

Monday, October 27

Morning: Assembly convenes at Fairmont Hotel. Keynote address by Dr. William P. Shepard, 2nd Vice President, Health and Welfare Division, Metropolitan Life Insurance Company; Assembly Panel discussions.

Noon: Assembly luncheon, Fairmont Hotel.

Evening: Dinner for Presidents and Board Chairmen of Heart Associations, Fairmont Hotel. Address by A. W. Robertson, past Chairman of the AHA Board of Directors

Tuesday, October 28

Morning: General meeting of Assembly to review Panel recommendations and elect officers and Board members. Installation of Francis L. Chamberlain, M.D., of San Francisco, as AHA President.

Registration

Advance registration forms for the Annual Meeting and Scientific Sessions may be obtained from the Association. Those who have registered as well as new registrants are required to check at the respective registration desks. Registration for the Scientific Sessions begins 8:00 A.M. Friday, October 24, at the Civic Auditorium. Registration for the Assembly begins 8:00 A.M., Monday, October 27, at the Hotel Fairmont.

Hospitality Lounge

The San Francisco Heart Association will maintain a Hospitality Lounge at the Fairmont Hotel from Friday, October 24 through Monday, October 27. The lounge will provide information on restaurants and places of interest. Special events for ladies include a boat cruise and a visit to Stanford University Campus.

Non-Members Welcome

Non-members as well as Heart Association members may attend the Scientific Sessions. A $3.00 registration fee, which entitles them to a copy of the printed abstracts, will be charged to non-members. Medical students, interns, residents, research workers and nurses will be welcome without payment of the fee.

Hawaii Scientific Sessions

The Hawaii Heart Association will conduct two days of scientific sessions and a tour of the islands, October 31-November 1, following the AHA Annual Meeting and Scientific Sessions. Arrangements to attend may be made through H. Douglas Chisholm, Associate Director of Administration, American Heart Association, 44 East 23rd Street New York 10, N. Y., or

directly through the American Express Company, 65 Broadway, New York, N. Y.

STROKES BOOKLET PUBLISHED; CEREBROVASCULAR MATERIAL IN *The Heart Bulletin*

A new booklet written to help the stroke patient and his family cooperate with the physician has been published by the American Heart Association and its affiliates. Entitled "Strokes, a Guide for the Family," the booklet gives specific information on how those who live with or care for the stroke patient at home can help in his recovery.

This guide emphasizes the importance of early rehabilitation and of close cooperation between the physician and members of the family in helping stroke patients regain many of their abilities. It gives specific suggestions for self-help devices for home use and also lists a number of sources which may be utilized during the rehabilitation process. Also included are recommendations for the families of patients requiring treatment over a long period of time and a discussion of the special problems of aphasia patients. Physicians may obtain copies for distribution to families of patients from local Heart Associations, or from the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

Clinical information on various phases of cerebrovascular disease is contained in the July-August issue of *The Heart Bulletin,* now sponsored by the AHA in cooperation with the National Heart Institute and the American Academy of General Practice. Included are articles on "Arterial Angiograph: Use in Diagnosis of Cerebrovascular Accidents," by Lois Collins, M.D.; "Speech Rehabilitation in Aphasia," by Philip R. Lee, M.D.; "Acute Cerebrovascular Accident," by Bryan Williams, M.D.; "Cerebrovascular Accidents and Myocardial Infarction," by William B. Bean, M.D.; and "Hypertensive Encephalopathy," by Irvine H. Page, M.D., A. C. Corcoran, M.D., and H. P. Dustan, M.D. *The Heart Bulletin* is published by The Medical Arts Publishing Foundation, 1603 Oakdale Street, Houston, Texas.

NEW CV RESEARCH INSTITUTE TO PRESENT SCIENTIFIC PROGRAM

A special scientific program will be presented on October 23 to mark the opening of the new Cardiovascular Research Institute of the University of California Medical School, San Francisco. The date was chosen to permit attendance by physicians who will be in San Francisco for the AHA's 31st Annual Scientific Sessions and 34th Annual Meeting, October 24-28.

Speakers on the program include Sir George Pickering, Regius Professor of Medicine, University of Oxford, England; Dr. I. Lyon Chaikoff, Professor of Physiology, University of California, Berkeley; Dr. Malcolm McIlroy, First Assistant, Institute of Cardiology, London; and Dr. Julius H. Comroe, Jr., Director of the new Cardiovascular Research Institute.

Tickets for the special scientific program are obtainable from the University of California Medical Center, San Francisco 22, Calif.

NEW FILM ON RHEUMATIC FEVER STRESSES MEDICATION, GUIDANCE

A new film which may serve as a visual aid to physicians addressing lay groups on the subject of rheumatic fever and its consequences is now available from local Heart Associations or through the AHA National Office. Entitled "Help for Young Hearts," the film emphasizes the importance of prophylaxis in preventing recurrences and of vocational guidance in post-rheumatic fever rehabilitation. It is the case history of a teenage girl with rheumatic heart disease who has been assisted by the demonstration project in vocational guidance for cardiac youngsters conducted jointly by the AHA, New York Heart Association and Vocational Advisory Service of New York. Produced and written by George C. Stoney, Potomac Films, for the American Heart Association and its affiliates, the 16 mm. black and white sound film runs 14½ minutes.

FRENCH ATHEROSCLEROSIS UNIT

The Cardiology Society of France has announced formation of the French Society for

the Study of Atherosclerosis. The new group, which will function as a section of the parent body, may be addressed at 16 Rue Ampère, Paris.

MEETINGS CALENDAR

October 20-23: American Academy of Pediatrics, Chicago. E. H. Christopherson, 1801 Hinman Avenue, Evanston, Ill.

October 24-28: American Heart Association Annual Meeting and Scientific Sessions, San Francisco. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

October 27-31: American Public Health Association, St. Louis. Berwyn F. Mattison, 1790 Broadway, New York 19, N. Y.

October 30: American Federation for Clinical Research, Midwestern Section, Chicago. John F. Mueller, Department of Medicine, Cincinnati General Hospital, Cincinnati 29, Ohio

November 6-8: Gerontological Society, Inc., 11th Annual Scientific Meeting, Philadelphia. Joseph T. Freeman, 1530 Locust Street, Philadelphia 2, Pa.

November 14-15: First Annual Symposium of Cinefluorography, Rochester, N. Y. George H. Ramsey, Department of Radiology, Strong Memorial Hospital, Rochester 20, N. Y.

December 12-13: American Federation for Clinical Research, Eastern Section, Boston. William B. Schwartz, New England Center Hospital, 171 Harrison Avenue, Boston 11, Mass.

January 22-24: American Federation for Clinical Research, Southern Section, New Orleans. Hillard M. Yow, Baylor University College of Medicine, Houston 25, Tex.

January 28-29: American Federation for Clinical Research, Western Section, Carmel, Calif. Richard J. Havel, University of California Medical Center, San Francisco 22, Calif.

ABROAD

November 30-December 3: Fourth Latin-American Congress of Angiology, Santiago, Chile. Juan Borzone Galvez, Cassila 10256, Santiago, Chile.

February 19-21: Central Surgical Association, Montreal, Canada. A. D. McLachlin, Victoria Hospital, London, Ontario, Canada.

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why all the fuss over potassium?

Many physicians will recall when safe but potent organomercurials were first introduced. At the time there was considerable worry about possible potassium loss. Patients were instructed to take foods rich in this mineral, and not infrequently potassium supplements also were advised. After enough experience was gained, it became evident that only the exceptional case could lose enough potassium to be concerned about. And with oral organomercurial diuretics this was practically never a problem.

Why revive the subject now? Because clinical experience with nonmercurial diuretics indicates most of them have such a specific effect on potassium that with their use very real problems must be faced. Enough potassium loss can lead to digitalis toxicity or to a classical overt hypopotassemia. Since a fair percentage of cardiacs who receive diuretics are also digitalized, this excess potassium excretion is clinically serious. Clinical experience is still too limited with some nonmercurial diuretics to say just how often such loss will occur—but warnings already have been sounded by some clinical investigators as to the need for potassium supplementation.

Experience in many patients, for many years, demonstrates that potassium loss is never a problem when NEOHYDRIN® is the oral diuretic. And there is no refractoriness to this effective oral organomercurial.

LAKESIDE

Circulation

OCTOBER 1958
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Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

31st Scientific Sessions of the American Heart Association
San Francisco, Calif., from October 24-26, 1958

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ANNUAL MEETING—1958

All scientific meetings are held at the Civic Auditorium

	SCIENTIFIC MEETINGS	
	Morning: 9:00 A.M.—12:30 P.M.	**Afternoon:** 2:00 P.M.—5:00 P.M.
FRIDAY OCTOBER 24	**(9:30) SCIENTIFIC SESSIONS FOR CLINICIANS** Symposia: Congenital Heart Disease Intravascular Clotting Peripheral Arterial Insufficiency Lectures: Evaluation of Chlorothiazide Traumatic Heart Disease Bacterial Endocarditis Panel: New Facts on Arrhythmias	
	SIMULTANEOUS SCIENTIFIC SESSIONS	
	JOINT SESSION—AMERICAN HEART ASSOCIATION AND AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS Genetic Factors in Cardiovascular Disease	**JOINT SESSION—COUNCIL ON CIRCULATION AND MICROCIRCULATORY CONFERENCE** Vascular Thrombosis Cerebral Circulation Vascular Reactivity
	Council on Circulation Council on Cardiovascular Surgery	Council on Rheumatic Fever and Congenital Heart Disease
	EVENING SESSION 8:00—11:00 Instrumental Study of the Heart and Circulation	
SATURDAY OCTOBER 25	**GENERAL SCIENTIFIC SESSION** Conner Memorial Lecture **Maintenance of Cardiorespiratory Functions by Extracorporeal Circulation** Brown Memorial Lecture **Hypersensitivity in Cardiovascular Disease**	**JOINT SESSION—AMERICAN HEART ASSOCIATION AND AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS** Panels: Emotional Factors in Atherosclerosis Hypertension and Atherosclerosis
SUNDAY OCTOBER 26	**SIMULTANEOUS SCIENTIFIC SESSIONS** Council on Clinical Cardiology Council for High Blood Pressure Research Council on Basic Science	Council on Community Service and Education Session for Physicians and the General Public Panels: Rewards of Research Rheumatic Fever Prevention
MONDAY OCTOBER 27	**ASSEMBLY PANELS** (Fairmont Hotel)	**ASSEMBLY PANELS** (Fairmont Hotel)

BUSINESS MEETINGS, LUNCHEONS AND DINNERS

Friday, October 24

COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE
Luncheon and Business Meeting
Peacock Court Mark Hopkins Hotel
12:45 P.M.

Saturday, October 25

COUNCIL ON CIRCULATION
Round Table Luncheon and Discussion
Fairmont Hotel
12:15 P.M.

Dinner
San Francisco Room Fairmont Hotel
6:15 P.M.

Sunday, October 26

COUNCIL ON BASIC SCIENCE
Luncheon and Business Meeting
Corinthian Hall Whitcomb Hotel
12:45 P.M.

COUNCIL ON CLINICAL CARDIOLOGY
Business Meeting
Arena Civic Auditorium
10:15 A.M.

COUNCIL ON COMMUNITY SERVICE AND EDUCATION
Luncheon and Business Meeting
Crystal Ballroom Whitcomb Hotel
12:30 P.M.

COUNCIL ON HIGH BLOOD PRESSURE RESEARCH
Business Meeting
Room 302 Civic Auditorium
12:30 P.M.

ANNUAL DINNER
American Heart Association
Gold Room Fairmont Hotel
7 P.M.

TUESDAY OCTOBER 28 9:30 A.M.—Gold Room of Fairmont Hotel
GENERAL ASSEMBLY OF THE AMERICAN HEART ASSOCIATION

9:30 A.M.—Gold Room of Fairmont Hotel

OCTOBER 28 GENERAL ASSEMBLY OF THE AMERICAN HEART ASSOCIATION

31st SCIENTIFIC SESSIONS

of the AMERICAN HEART ASSOCIATION

October 24-26, 1958

OCTOBER 28 9:30 A.M.—Gold Room of Fairmont Hotel
GENERAL ASSEMBLY OF THE AMERICAN HEART ASSOCIATION

CIRCULATION

OFFICIAL JOURNAL OF THE AMERICAN HEART ASSOCIATION

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PROCEEDINGS
of the
31st SCIENTIFIC SESSIONS

CIVIC AUDITORIUM, SAN FRANCISCO, CALIF.
OCTOBER 24-26, 1958

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1957-1958

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SESSION ON INSTRUMENTAL STUDY OF THE HEART AND CIRCULATION

CHARLES E. KOSSMANN, *New York*, CO-CHAIRMAN
VICTOR A. MCKUSICK, *Baltimore*, CO-CHAIRMAN
STANLEY BRILLER, *Philadelphia*
WILLIAM MILNOR, *Baltimore*

Scientific Sessions for Clinicians—arranged by the Program Committee of the Council on Clinical Cardiology

Session on Genetics and Panels on Arteriosclerosis—planned jointly with the American Society for the Study of Arteriosclerosis

Joint Session on Microcirculation—arranged by the Program Committee of the Council on Circulation and the Microcirculatory Conference

31st SCIENTIFIC SESSIONS
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FRIDAY
OCTOBER 24, 1958

SCIENTIFIC SESSIONS FOR CLINICIANS

Arranged by the Council on Clinical Cardiology

Arena—9:30 A.M. to 12:30 P.M.
2:00 P.M. to 5:00 P.M.

Chairman: **A. Carlton Ernstene, Clevèland, Ohio**

MORNING

Symposium on Congenital Heart Disease

9:30 to 11:00

9:30 **Approach to Diagnosis Without Recourse to Special Tests.** *Alexander S. Nadas, Boston, Mass.*

9:55 **Use of Special Tests in Diagnosis.** *S. Gilbert Blount, Jr., Denver, Colo.*

10:20 **Correlation of Clinical and Laboratory Findings —A Discussion.** *Alexander S. Nadas, Boston, Mass., S. Gilbert Blount, Jr., Denver, Colo., and C. Walton Lillehei, Minneapolis, Minn.*

10:35 **What's New in Treatment.** *C. Walton Lillehei, Minneapolis, Minn.*

11:00—INTERMISSION

Symposium on Treatment of Intravascular Clotting

11:10 to 12:30

1 10 **Anticoagulants and Clot Dissolvers.** *Sol Sherry, St. Louis, Mo.*

11:30 **Coronary Artery Heart Disease.** *John Martin Askey, Los Angeles, Calif.*

11:50 **Cerebral Artery Disease.** *Clark H. Millikan, Rochester, Minn.*

12:10 **Peripheral Venous Disease.** *Hugh Montgomery, Philadelphia, Pa.*

AFTERNOON

Current Subjects of Special Interest

2:00 to 3:00

2:00 **Clinical Evaluation of Chlorothiazide.** *Walter M. Kirkendall, Iowa City, Iowa*

2:20 **Traumatic Heart Disease.** *Loren F. Parmley, Jr., Washington, D. C.*

2:40 **The "Tough Case" of Bacterial Endocarditis.** *Ernest Jawetz, San Francisco, Calif.*

Panel Discussion on What's New in Arrhythmias

3:00 to 4:00

HERRMAN L. BLUMGART, *Boston, Mass., Moderator*
A. CARLTON ERNSTENE, *Cleveland, Ohio*
W. PROCTOR HARVEY, *Washington, D. C.*
R. BRUCE LOGUE, *Emory University, Ga.*
MAURICE SOKOLOW, *San Francisco, Calif.*
E. GRAY DIMOND, *Kansas City, Kans.*

4:00—INTERMISSION

Symposium on Peripheral Arterial Insufficiency

4:10 to 5:00

4:10 **Medical Aspects.** *Fay LeFevre, Cleveland, Ohio*

4:35 **Surgical Aspects.** *Michael E. DeBakey, Houston, Tex.*

FRIDAY MORNING
OCTOBER 24, 1958

SIMULTANEOUS SCIENTIFIC SESSIONS

JOINT SESSION: American Heart Association and American Society for the Study of Arteriosclerosis

Genetic Factors in Cardiovascular Disease — A Symposium

Polk Hall—9:00 A.M. to 12:30 P.M.

Chairmen: **Victor A. McKusick, Baltimore, Md., David Adlersberg, New York, N. Y.**

9:00 Hypertension.
Sir George Pickering, Oxford, England
Douglas R. Drury, Los Angeles, Calif.
and Caroline B. Thomas, Baltimore, Md.

9:45 Atherosclerosis.
Frederick H. Epstein, Ann Arbor, Mich.
Richard H. Osborne, New York, N. Y.
Arthur G. Steinberg, Cleveland, Ohio

10:30—INTERMISSION

10:40 Rheumatic Fever.
Paul A. Lembcke, Los Angeles, Calif.
May G. Wilson, New York, N. Y.

11:25 Congenital Malformations.
Victor A. McKusick, Baltimore, Md.
Catherine A. Neill, Baltimore, Md.

12:10 Discussion:
Opened by Antonio Ciocco, Pittsburgh, Pa.

Council on Circulation

Room 302—9:00 A.M. to 12:30 P.M.

Chairman: **William Goldring, New York, N. Y.**
Co-Chairman: **Travis Winsor, Los Angeles, Calif.**

9:00 Hereditary Hemorrhagic Telangiectasia and Pulmonary Arteriovenous Fistula: A Study of Six Generations of a Large Family. *Corrin H. Hodgson, C. Allen Good, Howard B. Burchell, and O. Theron Clagett, Rochester, Minn.*

9:15 Abnormalities of the Arterial Pulse Wave in Young Diabetic Subjects. *Arthur W. Feinberg, Great Neck, N. Y., and Henry Lax, New York, N. Y.*

9:30 Central and Peripheral Venous Pressure Correlations with Emotional Stimuli. *Kerr L. White, Dan A. Martin, Charles R. Vernon, and David H. Jones, Chapel Hill, N. C.*

9:45 Physiologic Study of the Chemoreceptor Mechanism in the Dog at Sea Level and at High Altitude (12,600 ft.). *Rutherford S. Gilliam, San Francisco, Calif. Julius T. Hansen, Ralph H. Kellog, Nello Pace, Berkeley, Calif., and Elizabeth M. Cuthbertson, San Francisco, Calif.*

10:00 Physiologic Evaluation of Chest Pain. *Norman Brachfeld, Joseph Messer, John Turner, and Richard Gorlin, Boston, Mass.*

10:15 Vasoconstriction and Vasodilation by Sphincter Muscles in the Capillary Circulation of the Heart. *Sidney Scherlis, and D. Vincent Provenza, Baltimore, Md.*

10:30—INTERMISSION

10:45 Observations Concerning Role of Pulmonary Lymph Flow in Pathogenesis of Pulmonary Edema. *Herman N. Uhley, Sanford E. Leeds, John J. Sampson, and Meyer Friedman, San Francisco, Calif.*

11:00 Pheochromocytoma: Evaluation of the Pharmacologic and Chemical Tests as an Aid to Diagnosis. *Grace M. Roth, Eunice V. Flock, and Walter F. Kvale, Rochester, Minn.*

11:15 Exaggerated Reactivity to Serotonin in Patients with Rheumatoid Arthritis and Related Diseases. *Arthur L. Scherbel, and John W. Harrison, Cleveland, Ohio*

11:30 Rate of Secretion of Aldosterone by the Adrenal Cortex in Normal Man and in Patients with Heart Failure, Nephrosis and Cirrhosis. *John H. Laragh, Stanley Ulick, and Seymour Lieberman, New York, N. Y.*

11:45 Postamputation Radiographic Evidence for Small Artery Obstruction in Arteriosclerosis. *Edward A. Edwards, Boston, Mass.*

12:00 Method for the Induction of Intravascular Structures. *Simon Rodbard, Buffalo, N. Y.*

12:15 Fibrinolytic (Plasmin) Therapy of Experimental Coronary Thrombi with Alteration of the Evolution of Myocardial Infarction. *Paul Ruegsegger, Irwin Nydick, Alvin Freiman, Robert V. P. Hutter, Nils Bang, Eugene E. Clifton, and John S. LaDue, New York, N. Y.*

Council on Cardiovascular Surgery

Larkin Hall—9:00 A.M. to 12:30 P.M.

Chairman: **Robert E. Gross, Boston, Mass.**
Co-Chairman: **Frank L. Gerbode, San Francisco, Calif.**

9:0[illegible] **Cardiopulmonary Bypass Complicated by Fat Emboli: An Experimental and Clinical Study.** *Guy Owens, Jesse E. Adams, and H. W. Scott, Jr., Nashville, Tenn.*

9:[illegible] **Surgical Treatment of Occlusive Lesions Occurring in Major Branches of Aortic Arch and Internal Carotid Arteries.** *E. Stanley Crawford, Michael E. DeBakey, Denton A. Cooley, and George C. Morris, Jr., Houston, Tex.*

9:[illegible] **Antifibrillatory Agents and Surgical Revascularizing Procedures Tested by Acute Closed-Chest Coronary Occlusion in the Pig.** *Joseph J. Garamella, Ruben Oropeza, Angelo Veloso, Ragaswamy L. Naidu, Lyle J. Hay, and James G. Andersen, Minneapolis, Minn.*

9:[illegible] **Left Ventricular–Right Atrial Shunts.** *Herbert N. Hultgren, Frank L. Gerbode, John Osborn, San Francisco, Calif., and Denis Melrose, London, England*

10:00 **Analysis of Clinical Results from the Surgical Creation of Pulmonary Stenosis in 35 Patients with Large Intracardiac Communications.** *W. Maddux Thompson, Jr., William H. Muller, Jr., and J. Francis Dammann, Jr., Charlottesville, Va.*

10:15 **Response of Infants with Large Ventricular Septal Defects to Banding of the Pulmonary Artery.** *Richard L. Fowler, Harold M. Albert, Rosalind Novick, Francis A. Puyau, and Claude C. Craighead, New Orleans, La.*

10:30 **Business Meeting**

10:45 **Clinical Use of Cardiac Pacemaker with Myocardial Electrode.** *Paul C. Hodges, Earl E. Bakken, and C. Walton Lillehei, Minneapolis, Minn.*

11:00 **Current Status of the Surgical Treatment of Acquired Aortic Stenosis.** *John E. Connolly, and David L. Bruns, San Francisco, Calif.*

11:15 **Correction of Aortic Regurgitation by Bicuspidization of the Valve.** *Charles P. Bailey, Philadelphia, Pa.*

11:30 **Hemodynamic Features in Congenital Aortic Stenosis and Their Modification by Operation.** *Eugene Braunwald, and Andrew G. Morrow, Bethesda, Md.*

11:45 **Correlation of Clinical and Experimental Phonocardiographic Criteria in the Diagnosis of Atrial and Ventricular Septal Defects.** *William M. Rogers, James R. Malm, Norman Thompson, James B. Harrison, and Ralph A. Deterling, Jr., New York, N. Y.*

12:00 **Coarctation of the Aorta: Observations on Growth of the Anastomotic Site Following Aortic Resection in Infants.** *Arthur J. Moss, Forrest H. Adams, Bernard J. O'Loughlin, and Wilfrid J. Dixon, Los Angeles, Calif.*

12:15 **Effect of Closure of Patent Ductus Arteriosus on Pressures in the Aorta, Pulmonary Artery, and Left Atrium.** *Richard M. Peters, Ernest Craige, Daniel T. Young, and Robert Zeppa, Chapel Hill, N. C.*

FRIDAY AFTERNOON
OCTOBER 24, 1958

Council on Circulation Business Meeting
Polk Hall—1:30 to 2:00 P.M.

SIMULTANEOUS SCIENTIFIC SESSIONS

JOINT SESSION: Council on Circulation with Microcirculatory Conference

Polk Hall—2:00 P.M. to 5:00 P.M.

Chairmen: **George E. Burch, New Orleans, La., Chester Hyman, Los Angeles, Calif.**

2:00 **Vascular Thrombosis.** *Samuel I. Rapaport, Los Angeles, Calif. and Edward Bloch, Cleveland, Ohio*

2:40 **Discussion.**

3:00 **Cerebral Circulation.** *Robert B. Aird, San Francisco, Calif., Murray C. Brown, and Edward J. Laskowski, Bethesda, Md.*

3:40 **Discussion.**

4:00—INTERMISSION

4:10 **Vascular Reactivity.** *Robert H. Goetz, Bronx, N. Y., and Benjamin W. Zweifach, New York, N. Y.*

4:50 **Discussion.**

Council on Rheumatic Fever and Congenital Heart Disease

Peacock Court, Mark Hopkins Hotel—Luncheon and Business Meeting: 12:45 to 2:00 P.M.

Larkin Hall—Session 2:00 to 5:00 P.M.

Chairman: **Currier McEwen, New York, N. Y.**

Co-Chairman: **Helen B. Taussig, Baltimore, Md.**

2:00 **Studies on the Pathogenesis of the Aschoff Body.** *Bernard M. Wagner, Philadelphia, Pa.*

2:15 **Studies on the Type-Specific Immune Response to Group A Streptococcal Infections in Chil-**

dren. *Alan C. Siegel, and Gene H. Stollerman, Chicago, Ill.*

2:30 **Clinical Picture of Combined Aortic and Mitral Stenosis.** *Gordon Katznelson, Robert Jreissaty, Gilbert E. Levinson, Walter H. Abelmann, and Laurence B. Ellis, Boston, Mass.*

2:45 **Combined Mitral Stenosis and Insufficiency Studied by Left Heart Catheterization.** *Elliot Rapaport, and Harold G. Richman, San Francisco, Calif.*

3:00 **Group A Streptococcal Cardiac Lesions in Rabbits.** *Robert E. Kalina, Philip L. Eckman, and Joel G. Brunson, Minneapolis, Minn.*

3:15—INTERMISSION

3:30 **Cardiac Ventriculography in the Study of Acquired and Congenital Heart Disease.** *Joseph F. Uricchio, J. Stauffer Lehman, William M. Lemmon, Edward A. Fitch, and William Likoff, Philadelphia, Pa.*

3:45 **Contrast Visualization of the Central Circulation by Selective Cine-Cardioangiography.** *F. Mason Sones, Jr., Cleveland, Ohio*

4:00 **Angiocardiographic Diagnosis of Aberrant Left Coronary Artery from Pulmonary Artery.** *Norman S. Talner, Aaron N. Stern, and Melvin M. Figley, Ann Arbor, Mich.*

4:15 **Congenital Absence of the Pulmonary Valve: Clinical and Pathologic Syndrome.** *Robert A. Miller, Harvey White and Maurice Lev, Chicago, Ill.*

4:30 **Pulmonary Hypertension Associated with Atrial Septal Defect.** *H. J. C. Swan, André David, and Robert O. Brandenburg, Rochester, Minn.*

4:45 **Differentiation of Interatrial Communications by Clinical Methods: Ostium Secundum, Ostium Primum, Common Atrium and Total Anomalous Pulmonary Venous Connection.** *James W. DuShane, William H. Weidman, and John W. Kirklin, Rochester, Minn.*

FRIDAY EVENING
OCTOBER 24, 1958

INSTRUMENTAL STUDY OF THE HEART AND CIRCULATION

Arena—8:00 to 11:00 P.M.

Co-Chairmen: **Charles E. Kossmann, New York, N. Y., Victor A. McKusick, Baltimore, Md.**

8:00 **Use of an Inert Radioactive Gas, KR^{85}, in the Detection and Quantification of Left-to-Right Shunts.** *Richard J. Sanders, and Andrew G. Morrow, Bethesda, Md.*

8:15 **Temperature Dilution Curves for the Detection of Cardiac Shunts.** *Milton H. Paul, Chicago, Ill., Abraham M. Rudolph, and Maurice B. Rappaport,* Boston, Mass.*

8:30 **Indicator-Dilution Method for Simultaneous Measurement of Pulmonary and Systemic Blood Flow in Patients with Left-to-Right Shunts.** *Earl H. Wood, Hiram W. Marshall, Newton C. Birkhead, James L. Russell, and André David, Rochester, Minn.*

8:45 **Comparison of the Differential Pressure Catheter-Computer Technic with other Methods for the Measurement of Instantaneous Pulsatile Blood Velocity.** *Samuel M. Fox, III, Alexander J. Mallos, Theodore Cooper, and Donald L. Fry, Bethesda, Md.*

9:00 **New Method for Intravascular Measurement of Instantaneous Linear Velocity and Volume Flow of Blood in the Intact Subject.** *A. MacDonell Richards, and Henry L. Taylor, St. Paul, Minn.*

9:15 **Accuracy of Continuous Photoelectric Recording of Dye Curves in the Measurement of Cardiac Output.** *David W. Richardson, Eugene M. Wyso, Allen M. Hecht, Richmond, Va., and Donald P. Fitzpatrick, Providence, R. I.*

9:30—INTERMISSION

9:45 **Instrumental Technics in Correlating Heart Sounds and Murmurs with Events of the Cardiac Cycle During Combined Right and Left Heart Catheterization.** *Alvin J. Gordon, Maurice Dunst, Leonard Steinfeld, and Paul A. Kirschner, New York, N. Y.*

10:00 **Production of Heart Sounds by the Cardiac Catheter.** *Frederic L. Eldridge, and Herbert N. Hultgren, San Francisco, Calif.*

10:15 **Acoustical Analysis of Coronary Blood Flow.** *G. Douglas Talbott, and David F. Moyer, Dayton, Ohio*

10:30 **Correlation of Electric and Anatomic Positions Using Biplane Angiocardiography and Conventional Electrocardiograms.** *Warren G. Guntheroth, Seattle, Wash., Carl-Olaf Ovenfors, and Danae Ikkos, Stockholm, Sweden*

10:45 **Analysis of the Circulation as a Self-Regulating System Using an Analog Computer.** *Homer R. Warner, Salt Lake City, Utah.*

*Deceased

SATURDAY MORNING OCTOBER 25, 1958

General Scientific Session on Applied Cardiovascular Research

Arena—9:00 A.M. to 12:30 P.M.

Chairman: **Robert W. Wilkins, Boston, Mass.**
Co-Chairman: **Edgar V. Allen, Rochester, Minn.**

9:00 **Preliminary Report of a Double Blind Evaluation of Ligation of the Internal Mammary Arteries.** *Leonard A. Cobb, George I. Thomas, Robert A. Bruce, and K. Alvin Merendino, Seattle, Wash.*

9:15 **Central Blood Volume as a Factor in the Regulation of the Circulation.** *James V. Warren, and Arnold M. Weissler, Durham, N. C.*

9:30

LEWIS A. CONNER MEMORIAL LECTURE

Maintenance of Cardiorespiratory Functions by Extracorporeal Circulation—With Consideration of Induced Cardiac Arrest

John H. Gibbon, Jr., Philadelphia, Pa.

10:15 **PRESENTATION OF THE ALBERT LASKER AWARD**

10:45 **Effectiveness of an Oral Penicillin Prophylaxis Program Against Rheumatic Fever Over 10 Years.** *Ruth Whittemore, New Haven, Conn.*

11:00—INTERMISSION

11:10

GEORGE E. BROWN MEMORIAL LECTURE

Role of Hypersensitivity in Cardiovascular Disease

Lewis Thomas, New York, N. Y.

11:55 **Rate of Decline in Myocardial Glycogen Following Arrest of Coronary Circulation: Effect of Pretreatment with Glucose and Insulin.** *John C. Wood, Guillermo S. Morales, and Hadley L. Conn, Jr., Philadelphia, Pa.*

12:10 **Coronary Disease in the Negroes of Haiti and the United States.** *Dale Groom, Edward E. McKee, Charleston, S.C., Vergniaud Pean, Port-au-Prince, Haiti, Charles Webb, Charleston, S.C., and Faye W. Grant, Evanston, Ill.*

SATURDAY AFTERNOON OCTOBER 25, 1958

JOINT PANELS: American Heart Association and American Society for the Study of Arteriosclerosis

Arena—2:00 to 5:00 P.M.

Emotional Factors in Atherosclerosis

2:00

LOUIS N. KATZ, *Chicago, Ill., Moderator*
E. COWLES ANDRUS, *Baltimore, Md.*
MEYER FRIEDMAN, *San Francisco, Calif.*
HENRY I. RUSSEK, *Staten Island, N. Y.*
STEWART G. WOLF, JR., *Oklahoma City, Okla.*

3:30—INTERMISSION

Association of Hypertension and Atherosclerosis

3:40

ARTHUR C. CORCORAN, *Cleveland, Ohio, Moderator*
NELSON W. BARKER, *Rochester, Minn.*
CLARK H. MILLIKAN, *Rochester, Minn.*
RUSSELL HOLMAN, *New Orleans, La.*
GEORGE C. GRIFFITH, *Los Angeles, Calif.*

SUNDAY MORNING OCTOBER 26, 1958

SIMULTANEOUS SCIENTIFIC SESSIONS

Council on Clinical Cardiology

Arena—9:00 A.M. to 12:30 P.M.

Chairman: **Francis L. Chamberlain, San Francisco, Calif.**
Co-Chairman: **William P. Thompson, Los Angeles, Calif.**

9:00 **Association of a Specific Behavior Pattern with Increases in Blood Cholesterol, Blood Clotting Time and Incidence of Clinical Coronary Disease.** *Meyer Friedman, and Ray H. Rosenman, San Francisco, Calif.*

9:15 **Limitations of Serum Enzyme Alterations in the Differential Diagnosis of Myocardial Infarction.** *Carlos F. Manso, and Felix Wróblewski, New York, N. Y.*

9:30 **Improved Technics for Arteriographic Study of Patients with Coronary Sclerosis.** *Alan P. Thal, L. Stephen Richards, Richard H. Greenspan, and Murray J. Murray, Minneapolis, Minn.*

9:45 **Selection of a Test for the Control of Oral Anticoagulant Therapy.** *W. Ford Connell, and George A. Mayer, Kingston, Canada*

10:00 **Mode of Death in Coronary Artery Disease: An Electrocardiographic and Clinical Pathologic Correlation.** *Herman K. Hellerstein, and David J. Turell, Cleveland, Ohio*

10:15 to 11:00 **Business Meeting**

11:00 **Thyroid Function in Euthyroid Patients with Paroxysmal Atrial Arrhythmias.** *George S. Kurland, Arnold Golodetz, and A. Stone Freedberg, Boston, Mass.*

11:15 **Vasopressor Therapy of the Cardiac Arrhythmias.** *Eliot Corday, John H. Williams, Herbert Gold, and Joshua Fields, Los Angeles, Calif.*

11:30 **Paroxysmal Ventricular Tachycardia: A Ten Year Study.** *George R. Herrmann, Galveston, Tex., Hi Myung Park, Taegu, Korea, and Milton R. Hejtmancik, Galveston, Tex.*

11:45 **Heart Disease in Friedreich's Ataxia: Incidence and Manifestations.** *Samuel H. Boyer, Victor A. McKusick, and Arthur W. Chisholm, Baltimore, Md.*

12:00 **Cardiopulmonary Dysfunction in Muscular Dystrophy.** *Kaye H. Kilburn, Herbert O. Sieker, Albert Heyman, and John Eagan, Durham, N. C.*

12:15 **Cardiac-in-Agriculture Demonstration.** *Lewis E. January, Joseph P. Stoikovic, Iowa City, Iowa, Thomas A. Robb, Washington, Iowa, and Warren L. Van Eschen, Cedar Rapids, Iowa*

Council for High Blood Pressure Research

Room 302—9:00 A.M. to 12:30 P.M.
Business Meeting 12:30 P.M.

Chairman: **Eric Ogden, Columbus, Ohio**

Co-Chairman: **Caroline B. Thomas, Baltimore, Md.**

9:00 **Evaluation of Chlorothiazide Alone in the Treatment of Moderately Severe and Severe Hypertension.** *Frank A. Finnerty, Jr., Joachim H. Buchholz, John Tuckman, and George T. Hajjar, Washington, D. C.*

9:15 **Extracellular Fluid and Plasma Volume Changes in Nonedematous Hypertensives After Prolonged Treatment with Chlorothiazide.** *Ilse M. Wilson, and Edward D. Freis, Washington, D. C.*

9:30 **Studies of the Content and Distribution of Sodium, Potassium and Water in Arterial Hypertension.** *Bertram M. Winer, Boston, Mass.*

9:45 **New Antihypertensive Drug, 1-Phenyl-2-Hydrazinopropane.** *Louis Gillespie, Jr., Luther L. Terry, and Albert Sjoerdsma, Bethesda, Md.*

10:00 **Arterial Rigidity in Hypertension.** *James Conway, Ann Arbor, Mich., Eileen Bussy, London, England, and Sibley W. Hoobler, Ann Arbor, Mich.*

10:15 **Depressive Reactions in Hypertensive Patients.** *Richard M. Quetsch, Richard W. P. Acher, Edward M. Litin, and Robert L. Faucett, Rochester, Minn.*

10:30—INTERMISSION

10:45 **Diagnostic Use of I^{131}-Diodrast in Hypertension Due to Unilateral Renal Disease.** *Jerome B. Block, and Belton A. Burrows, Boston, Mass.*

11:00 **Significance of Renal Function Tests in Renal Hypertension.** *Harriet P. Dustan, Eugene F. Poutasse, Arthur C. Corcoran, and Irvine H. Page, Cleveland, Ohio*

11:15 **Cause of Primary Hypertension.** *Milton Mendlowitz, Stanley Gitlow, and Nosrat Naftchi, New York, N. Y.*

11:30 **Hemodynamics in Labile Hypertension.** *Robert H. Eich, Richard J. Peters, and Richard H. Lyons, Syracuse, N. Y.*

11:45 **Acute Effects of Trimethidinium Methosulfate (WY-1395) on Blood Pressure, Cardiac Output, Renal Hemodynamics and Pulse Rate in Man.** *Walter M. Kirkendall, Mark L. Armstrong, David C. Funk, and Ernest O. Theilen, Iowa City, Iowa*

12:00 **Prevalence and Incidence of Coronary and Hypertensive Heart Disease in Strata of the Labor Force of a Chicago Industrial Organization.** *Jeremiah Stamler, Howard A. Lindberg, David Berkson, Aaron Shaffer, Albert Poindexter; with the assistance of Wilda Miller, Mildred Colwell, and Yolanda Hall, Chicago, Ill.*

12:15 **Relationships of Hypertension and Experimental Pyelonephritis in the Rat.** *Alvin P. Shapiro, Pittsburgh, Pa.*

Council on Basic Science

Larkin Hall—9:00 A.M. to 12:30 P.M.

Chairman: **James V. Warren, Durham, N.C.**

Co-Chairman: **Lysle H. Peterson, Philadelphia, Pa.**

9:00 **Continuous Measurement of Thoracic-Aortic Flow During Head-Up Tilt in Man.** *Ra[illegible]*

mond E. Brow, Darryl K. Foerster, H. J. C. Swan, and Earl H. Wood, Rochester, Minn.

9:15 **Effects of Isoproterenol on Peripheral Venous Tone and Transmural Central Venous Pressure in Man.** *John W. Eckstein, and William K. Hamilton, Iowa City, Iowa*

9:30 **Measurement of Regional Blood Flow in Dog Intestine.** *Eugene Grim, and Esten O. Lindseth, Minneapolis, Minn.*

9:45 **Potential Changes Attending the Excitation Process in the Atrioventricular Conduction System of Bovine and Canine Hearts.** *Raymond D. Pruitt, Hiram E. Essex, and Howard B. Burchell, Rochester, Minn.*

10:00 **Early Metabolic Alterations and Fine Structure Changes in Myocardial Fibers Irreversibly Injured by Ischemia.** *William B. Wartman, Robert B. Jennings, John P. Kaltenbach, Hisako O. Yokoyama, and Gunther F. Bahr, Chicago, Ill.*

10:15 **Extracted Heart Muscle Preparation with Respiratory and Phosphorylative Activity.** *Richard J. Guillory, and Wilfried F. H. M. Mommaerts, Los Angeles, Calif.*

10:30 **High Energy Phosphate Metabolism in the Arrested Heart.** *Vincent L. Gott, Marilyn M. Bartlett, and John A. Johnson, Minneapolis, Minn.*

10:45—INTERMISSION

11:00 **Lipid and Acid Polysaccharide Relationship in Human Aortas.** *Frederick T. Zugibe, and Kenneth D. Brown, Downey, Ill.*

11:15 **Influence of Hyperthermia and Hypothermia on the Ventricular Fibrillation Threshold of Dogs.** *Clifford M. Phibbs, and Lloyd D. MacLean, St. Paul, Minn.*

11:30 **Effect of Carbon Dioxide on the Pulmonary Vascular Bed.** *Felice Manfredi, and Herbert O. Sieker, Durham, N. C.*

11:45 **Role of the Liver in Digitalis-Induced Electrolyte Shifts.** *Bernard Lown, Gerald H. Whipple, William C. Shoemaker, Boston, Mass., Louis C. Craig, Charlottesville, Va., and Samuel A. Levine, Boston, Mass.*

12:00 **Evidence for the Countercurrent Multiplier System for Urine Concentration.** *Carl W. Gottschalk, and Margaret Mylle, Chapel Hill, N. C.*

12:15 **Influence of Atrial Stretching and Vagal Block on Aldosterone Secretion.** *Charles H. Anderson, Michael McCally, and Gordon L. Farrell, Cleveland, Ohio*

Corinthian Hall, Whitcomb Hotel—Luncheon and Business Meeting: 12:45 to 2:00 P.M.

SUNDAY AFTERNOON
OCTOBER 26, 1958

COUNCIL ON COMMUNITY SERVICE AND EDUCATION

Crystal Ballroom, Whitcomb Hotel—Luncheon and Business Meeting: 12:30 to 1:45 P.M.

SPECIAL SESSION FOR PHYSICIANS AND THE GENERAL PUBLIC

Arena—2:00 to 5:00 P.M.

Panel: Rewards of Research

2:00 to 3:30

Chairman: **Walter S. Priest, Chicago, Ill.**

LOUIS N. KATZ, *Chicago, Ill., Moderator*
JULIUS H. COMROE, JR., *San Francisco, Calif.*
EMILE F. HOLMAN, *San Francisco, Calif.*
JOHN G. SMITH, *Rocky Mount, N. C.*
MILTON SILVERMAN, *San Francisco, Calif.*
JESSE H. STUART, *Riverton, Ky.*

Discussion

INTERMISSION

PANEL: Rheumatic Fever Prevention

3:45 to 5:00

Co-sponsored by the Council on Rheumatic Fever and Congenital Heart Disease

Chairman: **Currier McEwen, New York, N. Y.**
Co-Chairman: **Oglesby Paul, Chicago, Ill.**

Secondary Prevention

3:45 **Scientific Basis for Rheumatic Fever Prevention.** *Lowell A. Rantz, San Francisco, Calif.*

4:00 **Secondary Prevention Programs in a Metropolitan Area.** *Katharine Dodge Brownell, New York, N. Y.*

4:15 **Secondary Prevention Programs in a Rural Area.** *J. Gordon Barrow, Atlanta, Ga.*

4:30 **Discussion**

Primary Prevention

4:40 **Study of City-Wide Methods.** *Alan C. Siegel, Chicago, Ill.*

Discussion opened by Gene H. Stollerman, Chicago, Ill.

ABSTRACTS OF PAPERS

LEWIS A. CONNER MEMORIAL LECTURE

Maintenance of Cardiorespiratory Functions by Extracorporeal Circulation, with Consideration of Induced Cardiac Arrest

John H. Gibbon, Jr., Philadelphia, Pa.

The clinical use of an extracorporeal circulation to maintain the cardiorespiratory functions of a patient during open cardiotomy is now well established. Nevertheless, there remains problems which require solution and new fields have been opened up for exploration.

The role played by pressor receptors in the great veins and atriae in regulating vasoconstriction should be studied during complete bypass of the heart and lungs. Reflexes may arise from these receptors causing blood to become pooled in certain vascular areas, resulting in a diminished return of blood to the venae cavae. The arterialized blood from the circuit is usually returned through a centrally directed cannula in a common femoral artery. The piezometric effect of reversal of flow through the aorta upon flow through the aortic branches has not yet received adequate study.

The gas exchange in the extracorporeal circuit is currently accomplished by exposing a film of blood to oxygen. The blood film is established on vertical screens, revolving discs, etc., or on bubbles of oxygen. In the two former methods, it is easy to maintain a normal carbon dioxide tension in the blood. In the bubble oxygenators, excessive foaming is prone to occur if the ratio of the flow of oxygen to the flow of blood is high enough to prevent an abnormal rise in carbon dioxide tension. Abnormally high tensions of oxygen in the plasma have been shown to be undesirable and even toxic. Such high tensions are particularly apt to occur in the bubble type oxygenators.

During the early postoperative hours following complete bypass of the heart and lungs with an extracorporeal circuit, the oxygen saturation of the arterial blood is apt to fall and the carbon dioxide tension to rise. More than one etiologic factor may be involved in this postoperative pulmonary dysfunction: inadequate depth of respiration from postoperative pain, overhydration or hypervolemia, or a marked change in the *milieu interieur* of the alveolar and pulmonary capillary epithelium when the normal flow of blood through the pulmonary capillaries is absent. The metabolic acidosis existing at the end of the period of perfusion is usually mild and frequently no greater than that existing after operations of similar magnitude but without the extracorporeal circuit. The more nearly the blood flow through the circuit approaches the normal resting cardiac output under anesthesia, the less the metabolic acidosis which is observed.

Operations within the heart under direct vision can be performed more swiftly and easily when the heart is not beating. Cardiac arrest may be produced by rapid perfusion of the coronary circulation with solutions of potassium salts or acetylcholine, or by arresting the blood flow through the coronary arteries. The metabolism of the myocardium is greatly reduced when contractions cease, but the length of the safe period of cardiac arrest under normal body temperature has not been determined. Whether "anoxic" arrest," with its accumulation of acid metabolites, is more or less harmful than the more rapid arrest produced by the use of potassium salts or acetylcholine remains to be determined. The sensitivity of the specialized fibers of the bundle of His to anoxia should be explored. During cardiac arrest the difference in the rates of cooling of the thick-walled ventricle, as opposed to the thin-walled atria, has not been measured. Prolongation of the safe period of arrest by perfusion of the heart with cold solutions remains to be explored. Many hitherto unexplored aspects of that extraordinary muscular organ, the heart, now lie open for investigation.

GEORGE E. BROWN MEMORIAL LECTURE

Role of Hypersensitivity in Cardiovascular Disease

Lewis Thomas, New York, N. Y.

The possibility that lesions of the human heart and blood vessels may be brought about by hypersensitivity is supported, by indirect evidence, in rheumatic fever, polyarteritis, nodosa, and disseminated lupus erythematosus. In each case, however, conclusive data to settle the issue remain beyond reach. Meanwhile, speculative claims are being made for an allergic basis for various other cardiovascular disorders, including idiopathic myocarditis and even coronary thrombosis.

A critical evaluation of the existing information bearing on the role of hypersensitivity in the pathogenesis of vascular lesions will be attempted in this lecture. The present status of several laboratory models in experimental pathology, indicating the involvement of immune mechanisms in tissue damage, will be reviewed, with particular reference to disease states in which "auto-antibodies" seem to be implicated.

Abstracts are printed alphabetically according to the senior authors.

**Research Fellow, American Heart Association, 1957-1958.*
†Established Investigator, American Heart Association, 1957-1958.

Fundamental Factors Involved in Regulating the Contractile Strength of the Heart

Bernard C. Abbott and Wilfried F.H.M. Mommaerts,† Los Angeles, Calif.

A more penetrating analysis of variations in the strength of a heart beat than has hitherto been attempted must be based upon consideration of the events between stimulus and contraction. According to the concepts developed by A. V. Hill and his school, contraction in skeletal muscle is preceded by the so-called "active state." The contractile strength of a twitch is limited by the fact that the active state declines before contraction reaches its maximum. Hence, lengthening the active state strengthens the twitch, and the current tendency in skeletal muscle physiology is to regard the duration of the active state as the main variable factor.

We have applied analyses along similar lines to the papillary and trabecular muscles of mammalian heart, with the primary aim of describing the inotropic variations known as the staircase effect and postextrasystolic potentiation. We found that a strengthening of the beat in these cases is never due to a lengthening of the active state; on the contrary, its duration becomes shorter as the potentiation develops during the ascent of the staircase. Instead, 2 other possibilities are to be considered: an intensification of the active state itself, and a change in the force-velocity relation so that a greater fraction of the possible tension is developed within the available time. Our measurements have shown such a change in the intrinsic velocity, but we have not yet been able to decide whether this is the entire cause of potentiation, or whether it, like potentiation, is caused by an increased amplitude of the active state.

Tolerance to Acetylstrophanthidin in Normal Dogs and in Dogs With Chronic Congestive Heart Failure

Robert J. Adolph and Harry A. Bliss, Chicago, Ill.*

The clinical impression that a normal heart tolerates considerably larger doses of digitalis than does a decompensated heart was substantiated in a controlled animal experiment.

Fifteen normal dogs and 6 dogs with chronic congestive heart failure, surgically induced months previously by creation of tricuspid insufficiency and pulmonary stenosis, were anesthetized with intravenous sodium pentobarbital. The electrocardiogram was observed before and for 18 minutes after the slow intravenous administration of acetylstrophanthidin. Dogs with heart failure received 0.025-0.034 mg. of the drug per Kg. ascites-free body weight. This weight was measured when the animal was sacrificed an average of 9 days later. Normal dogs received 0.03 mg. acetylstrophanthidin per Kg. body weight.

Twelve normal dogs showed no electrocardiographic evidence of toxicity. Three normal dogs demonstrated probable minimal toxicity, 1 dog having 1 and another having 6 nonsuccessive ventricular premature contractions. The third animal had 2 nonsuccessive ventricular premature contractions and a blocked sinus beat. Five dogs in heart failure developed major toxicity to acetylstrophanthidin. Runs of ventricular tachycardia lasting several minutes occurred in 4 dogs, and persistent 2:1 A-V block appeared in the fifth. One dog with heart failure showed no toxicity. The probability of this difference in incidence of toxicity occurring by chance alone is less than 5 per cent. The difference in severity of toxicity is even more striking.

No correlation was found between electrocardiographic evidence of toxicity and the serum potassium concentration, determined both before and 8 minutes after acetylstrophanthidin administration.

Effect of Cytochrome C on Serum Cholesterol in Rabbits

Rudolph Altschul, Saskatoon, Saskatchewan, Canada

In pursuing the theory that serum cholesterol can be lowered by stimulating oxidative processes in the body, relatively large doses of nicotinic acid —a prosthetic group of the respiratory co-enzymes

SELECTION OF PAPERS: Abstracts of papers and exhibits submitted were evaluated by the Program Committee of the appropriate council and the Subcommittee on Exhibits of the American Heart Association. The final selections were made by the Committee on Scientific Sessions Program of the American Heart Association on the recommendations of the Council Program Committees. In accordance with committee policy, no senior author was included on the program more than once, nor were papers accepted if the author had submitted a proposal for a scientific exhibit on the same topic.

DPN and TPN—were given to humans and rabbits. Nicotinic acid is said to increase oxygen saturation of the venous blood in normals and, in heart failure, also that of the arterial blood. Following its intake, DPN and TPN increase in the blood. Treatment with nicotinic acid decreased serum cholesterol and, in rabbits, inhibited experimental atherosclerosis. These findings have been confirmed by others. When we injected rabbits with DPN, TPN, peroxidase or catalase, which latter two also belong to the oxidation system of the body, the decrease in serum cholesterol which followed after 5-6 hours was, so far, not significant. On the other hand, single intravenous, intramuscular or subcutaneous injections of cytochrome C lowered serum cholesterol in normal rabbits significantly. In rabbits in which the serum cholesterol had been raised previously (range 776-2261 mg. per cent), the absolute decrease (average 80 mg. per cent) was larger than in normal animals, but the per cent decrease, if compared to diurnal variations, was not significant. This could be explained by either insufficient dosage of cytochrome C, or by weak responsiveness on account of tissue damage.

Influence of Atrial Stretching and Vagal Block on Aldosterone Secretion

Charles H. Anderson, Michael McCally, and Gordon L. Farrell,† Cleveland, Ohio

In previous work, it has been demonstrated that the secretion of aldosterone by the adrenal is markedly affected by distension of the right atrium. In control dogs, the secretion rate of aldosterone, as determined by isolation of the steroid from adrenal venous blood, was 48.9 ± 2.4 (standard error) μg. per 100 Kg. body weight per hour. Open chest procedures or stretching of the left atrium with sutures between the atrium and chest wall were without significant effect on this rate (43.3 ± 4.3 and 42.3 ± 6.0, respectively). Stretching the right atrium diminished the aldosterone secretion rate to approximately 50 per cent of the control value (23.8 ± 3.5, significant $p < .01$). In an effort to define the afferent pathways subserving this effect (presumably a reflex arising in the right atrium), vagal block was accomplished by cooling the nerves to 0 C. for a 1-hour period prior to collection of adrenal venous blood. In a parallel series of 5 control animals, the secretion rate was 33.9 ± 6.3 μg. per 100 Kg. body weight per hour; after vagal cooling (7 dogs) the rate was 17.8 ± 4.3. The depression in steroid output is significant ($p < .05$). Although interpretation of these results is somewhat difficult, it seems probable that the vagi carry fibers which act tonically to stimulate aldosterone secretion, part of which may arise in the atria. The data are consistent with the concept that tonically discharging atrial receptors are inhibited by stretching, although further experiments are clearly necessary to elucidate the physiological mechanism involved.

Antifibrillary Agents in Experimental Hypothermic Surgery

E. T. Angelakos, F. H. Anlyan, F. S. Pope, and A. H. Hegnauer, Boston, Mass.

Previous studies have demonstrated that quinidine and certain antihistaminics are very effective in protecting dogs from spontaneous hypothermic ventricular fibrillation (VF). Several of these compounds were therefore tested against VF due to right ventriculotomy performed at 20-25 C.; pH was controlled via artificial respiration from onset of cooling. In unselected operated dogs, 40-60 per cent fibrillate during surgery. In experiments employing multiple exploration of the incised ventricle combined with electrical defibrillation it is possible to *predetermine* the fibrillators, *and on these* to test efficacy and duration of drug action. Repeated explorations at various time intervals after drug administration revealed that single i.v. injections of quinidine (10 mg./Kg.) afforded 100 per cent and 90 per cent protection in 10 dogs for 15 and 30 minutes postinjection, decreasing to 80 per cent and 50 per cent at 45 and 60 minutes. Repeated explorations in such animals receiving only saline injections resulted in 100 per cent VF in 10 dogs at all time intervals.

Screening experiments with Histadyl, Antergan, Pronestyl, Ambonestyl and Ro2-7302, revealed that none had effects comparable to quinidine. Thus no strict parallelism exists between pharmacologic protection against spontaneous vs. surgically induced hypothermic VF.

Statistical Associations Between International Coronary Heart Disease: Death Rates and Certain Environmental Factors

Morton Archer and Norman Jolliffe, New York, N. Y.

Associations have been determined by use of simple and multiple correlation technics between international death rates for coronary heart disease and various environmental factors, dietary and nondietary. The difference between the methods used in this study and those others which have used the same data lies primarily in the fact that, in this instance, the distinction has been made between the saturated and unsaturated (mono- and polyethenoid) types of fat.

For the 20 countries for which comparable data are available, it is shown that the most important

factors in explaining the variances in coronary heart disease death rates between nations are the intakes of (1) saturated fat and (2) animal protein expressed as a proportion of total calories. Saturated fat intake alone explains 68 per cent of the total variance, while animal protein explains 64 per cent. The high correlation between intake of saturated fat and animal protein explains the overlap in the explained variance. This is but one example of the large proportion of high correlations between the independent factors considered.

It is pointed out that the chief value of this type of epidemiologic analysis (aside from lending or withholding support for a theory) is to provide leads for further investigation by laboratory and/or clinical methods. Substantiation of effectiveness by one or another of these methods is necessary in order to confirm the true importance of a factor. Such laboratory confirmation appears to exist in the instance of saturated fats but not for animal protein within the limits of protein adequacy and amino-acid balance.

Effect of Forced Inhalation of Tobacco Smoke on the Electrocardiogram of Normal and Tobacco-Sensitized Rabbits

Robert N. Armen, Clarksburg, W. Va., and Sheldon Cohen, Wilkes Barre, Pa.

This paper discusses the electrocardiographic patterns obtained from groups of rabbits subjected to various challenging experiments. Normal, as well as tobacco-protein-sensitized rabbits, are used and the results are compared and contrasted. Technics are described for the sensitization of the animals, as well as for obtaining satisfactory electrocardiograms. The challenging experiments include forced inhalation of cigar smoke, mechanical suffocation, overdosage of intravenous Nembutal and the intravenous injection of a tobacco-protein extract.

Animals are subjected to these experiments in a simple wooden chamber in which they are effectively exposed to various concentrations of cigar-smoke-laden air, under light Nembutal anesthesia, and while they are connected to an electrocardiograph by special electrodes attached to their feet. Cigar smoke is introduced into the "head-chamber" by forcing a stream of compressed air through a lighted cigar.

The electrocardiographic responses are described and possible mechanisms responsible for death and the electrocardiographic abnormalities are discussed:

1. Prior sensitization to tobacco-protein does not appear to influence the cardiovascular responses of these animals to the various challenging situations.

2. The significant electrocardiographic abnormalities noted are: sinus bradycardia, various degrees of A-V block, A-V disassociation, sinus block, and eventual ventricular asystole, as well as minor T-wave abnormalities.

3. These cardiovascular effects do not appear to be due to anaphylaxis or an immunologic reaction.

4. Anoxia, mediated through various mechanisms, appears to be the common denominator responsible for death of the animals and the electrocardiographic abnormalities.

Contribution of Phonocardiography to the Assessment of the Physiology of Acyanotic Congenital Heart Disease

Marvin L. Auerback, Maurice Sokolow, and Ellen Simpson, San Francisco, Calif.

The recent advances in cardiovascular surgery make it imperative that patients with congenital heart disease be discovered and treated before they become inoperable. Phonocardiography is one method of selection of the patients who most urgently need cardiac catheterization and allied studies.

Using a highly sensitive and critically-damped phonocardiograph machine built at the University of California, we have recorded heart sounds and murmurs in over 200 children and young adults with proven congenital heart disease.

Our studies have shown that the various acyanotic congenital heart lesions produce murmurs and heart sounds that are relatively constant in timing, configuration and location. More importantly, we have found that with the appearance of certain pathophysiologic states, such as pulmonary hypertension, these murmurs and heart sounds change in a predictable manner.

Experience in over 50 cases of ventricular septal defect, with varying degrees of pulmonary hypertension, has shown that the typical pansystolic murmur becomes gradually converted into a crescendo-decrescendo murmur, and ultimately into a faint decrescendo systolic murmur as the right ventricular pressure mounts. Patients with atrial septal defect, patent ductus arteriosus, and pulmonic stenosis, complicated by varying degrees of right ventricular hypertension, have demonstrated equally striking phonocardiographic patterns.

Study of the phonocardiographic changes often enable the clinician to make an accurate assessment of the physiologic disturbance occasioned by the cardiac defect, and select those patients who are in greatest need of further intensive study or treatment.

Correction of Aortic Regurgitation by Bicuspidization of the Valve

Charles P. Bailey, Philadelphia, Pa.

Definitive correction of aortic insufficiency remained unattainable surgically until the circulatory bypass technics became acceptably perfected. Today it is feasible to maintain myocardial and bodily vigor while the ascending aorta is opened for the methodical performance of a plastic procedure upon the aortic valve.

Following a prolonged experimental program, the principle of conversion of the regurgitant tricuspid aortic valve into a competent bicuspid one was applied clinically on July 19, 1956. Subsequent logical modifications in concept and in surgical technic have brought the operative procedure to a high level of efficiency and safety. Over 30 patients suffering from aortic insufficiency have been operated to date.

The 3 major types of the disease are those due to dilatation of the aortic root, those due to prolapse or inversion of a cusp, and those with coexisting aortic stenosis.

A distinctly different operative technic has been developed for each of these conditions. However, the physiologic correction is dependent upon the conversion of the valve into a bicuspid one by a plastic surgical procedure which utilizes existing intrinsic or contiguous living structures. Undoubtedly some impedance to blood flow is imposed upon the circulation by this bicuspidization; however, it appears to be clinically acceptable.

Incidence and Significance of Postoperative Electrocardiographic Changes: A Serial Study

William Baird, West Haven, Conn., Daniel Kahn, Meriden, Conn., Woodrow W. Lindenmuth, and Massimo Calabresi, West Haven, Conn.

Preoperative and 24-hour postoperative electrocardiograms were taken in a series of 500 consecutive surgical patients above the arbitrary age of 45. Results were classified under 3 categories: (1) no changes in the electrocardiogram; (2) diagnostic electrocardiographic changes; (3) "nonspecific" electrocardiographic changes. All patients with electrocardiographic changes were followed with serial tracings; these patients and all other patients with preoperative or postoperative cardiac findings were followed by the cardiologist.

The third group (initially "nonspecific" changes) resolved itself in 3 subgroups: (1) initial changes of localized myocardial damage; (2) transitory changes of short duration, not accompanied by other findings and presumably devoid of meaning of cardiac damage beyond the stress of the procedure; (3) more persistent changes with slow return to the initial electrocardiogram. The significance of these findings may become apparent only after prolonged observation.

This study reflects the importance of the routine preoperative electrocardiogram. The empirical experience here presented should prove helpful in the clinical evaluation of postoperative electrocardiograms obtained because of suspected cardiac complications. The "nonspecific" quality of the electrocardiographic findings is stressed by these observations. The need of further studies correlating electrocardiographic and pathologic findings is indicated. Our experience shows the value of close cooperation of the cardiologist with the surgeon in the evaluation and in the management of "cardiac poor risk" patients during surgery and in the preoperative and postoperative periods.

Anastomosis of Systemic to Coronary Artery: Experimental Study

Norman H. Baker, John H. Grindlay, John W. Kirklin, and Jesse E. Edwards, Rochester, Minn.

Previous investigators have found that in 86 of 125 (69 per cent) occlusions in the major coronary arteries occurred in their proximal 4 cm.

The diameter of the proximal 4 cm. of the major coronary arteries was measured, therefore, in adult human hearts. The average outside diameter was 4.2 mm. Autogenous arterial grafts with outside diameters of 3 mm. were then used to bridge defects in the carotid arteries of dogs. In a series of 20 animals, 16 (80 per cent) of the grafts remained patent and functioning when examined 2 months later.

In 16 mongrel dogs, a standard procedure was used for a systemic-to-coronary arterial shunt. The internal mammary artery was anastomosed end-to-end with the left circumflex coronary artery over a polyethylene catheter. The catheter was removed just before completion of the anastomosis. Thirteen of the 16 animals survived the initial surgical procedure. Five animals survived 2 months or longer. Coronary arteriograms were taken 2 to 4 months later on 4 of the surviving animals. The outside diameter of the vessels at the anastomosis was 1 to 2 mm. There were 2 successful shunts of 2 and 4 months' duration.

In this study, the coronary arteries of dogs were less than half the size of human coronaries. The extreme smallness of the vessels probably accounts for the unsuccessful shunts obtained in dogs.

Increased Clearing Factor Response in Laennec's Cirrhosis and Its Relationship to Serum Lipids and Hypoalbuminemia

Saul P. Baker, Harold Levine, Liebert Turner, and Alvin Dubin, Chicago, Ill.

decreased heparin-activated clearing factor (lipoprotein lipase) response has been associated with coronary atherosclerosis. Utilizing a standardized in vitro method, a significantly increased clearing factor response has been observed in patients with primary diagnoses of chronic alcoholism and/or Laennec's cirrhosis. Inasmuch as a lesser incidence of atherosclerosis has been postulated in Laennec's cirrhosis, more extensive studies have been made on a larger group, comprising 72 patients to date with various types of hepatic pathology or jaundice. Twenty-seven of these subjects demonstrated clinical and laboratory evidence of Laennec's cirrhosis. Comprehensive laboratory evaluation of hepatic status included BSP and serum bilirubin.

These studies have confirmed the presence of an increased clearing factor response in Laennec's cirrhosis. Furthermore, there appears to be no correlation between clearing factor and levels of total serum lipids, or lipid phosphorus, these being within the normal range. Serum total cholesterol generally ranged below 200 mg. per 100 ml. Per cent of serum cholesterol esters was almost uniformly low, being below 50 per cent (below 75 mg. per 100 ml.). The serum cholesterol/lipid phosphorus ratio appears to be related to the clearing factor response. Hypoalbuminemia produced no depressant effect upon clearing factor, the greatest response being observed with serum albumin below 3.0 Gm. per 100 ml.

It is suggested that the increased clearing factor response in patients with Laennec's cirrhosis is related to their parenchymal liver cell damage, and that an interrelationship may exist between clearing factor response, cholesterol/lipid phosphorous ratio, lipid metabolism, and atherosclerosis.

Wedge Pulmonary Arteriography: Application in Congenital and Acquired Heart Disease

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A clinical method for visualizing radiographically the smaller pulmonary arteries and arterioles has been devised. A cardiac catheter is wedged into a pulmonary artery and an x-ray exposure made after injecting 3 ml. of radiopaque dye.

This technic has been applied in 40 patients with cardiac defects showing hemodynamic pattern of: (1) normal pulmonary artery pressure and flow; (2) normal or slightly increased pulmonary artery pressure and increased pulmonary blood flow; (3) high pulmonary artery pressure and decreased pulmonary flow; and (4) increased pulmonary artery pressure due to increased left atrial pressure. The arteriograms of these patients have been correlated with the hemodynamic studies and with lung specimens obtained at surgery or autopsy.

The normal pulmonary arteriogram shows abundant arborization of small arteries of 200-2,000 micra, with filling of smaller arterioles and capillaries producing distinctive background markings. The abnormal pulmonary arteriogram of patients with pulmonary hypertension and balanced or right-to-left shunt, shows sparsity of arborization of these small pulmonary arteries, abrupt termination of 800-1,200 micra arteries, or narrowing of these arteries into fine, tortuous channels without normal capillary filling. The cases with normal pulmonary artery pressure and high pulmonary flow show no changes as compared with the normal. The abnormal arteriogram shows an excellent correlation with the histologic picture of intimal proliferation and occlusive changes seen in the small pulmonary arteries of those patients with high pulmonary artery pressure and decreased pulmonary blood flow. The arteriograms of patients with pulmonary artery hypertension due to left heart obstruction show decreased arborization of an intermediate degree.

The wedge pulmonary arteriograph provides a clinical method for demonstrating occlusive pulmonary vascular changes in patients with cardiac defects. The method should prove useful in selecting patients for surgical repair of these defects.

Heart and Lungs as a Common Chamber During Fibrillation and Extracorporeal Circulation

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Substitution for the fibrillating canine heart has been maintained for prolonged periods with the pump oxygenator. Peripheral vessel cannulation and closed chest fibrillation and defibrillation have permitted the study of retrograde flow in the heart and lungs.

At the onset of ventricular fibrillation, blood flow continues from right to left. Equilibrium is reached when arterial pressure has fallen to static levels. With extracorporeal circulation and rising intra-aortic pressure, the aortic valve closes. The establishment of differential pressure gradient in the inferior vena cava causes retrograde flow. Transbronchial catheterization of the left atrium and jugular cannulation of the right atrium reveal a left to right average gradient of 3 cm. of saline. Immediate resumption of antegrade flow occurs when venous pressure in the right heart is allowed to rise with continued arterial inflow. Failure to reduce right heart pressure results in fatal pulmonary hemorrhage.

During retrograde flow, radioactive material injected into the left atrium is recovered in the pul-

monary artery and right heart. Aortic injection is recovered in left atrium and pulmonary artery.

Determination of left ventricle pressure via percutaneous catheter revealed static values equivalent to that in the left atrium. The atria maintain a regular rhythm independent of the fibrillating ventricles. Evidence of a common chamber is seen in the intraventricular transmission of the atrial pressure wave.

During fibrillation, all cardiac valves except the aortic are incompetent. Blood does not accumulate in the left ventricle. Bronchial flow into the left atrium is returned through the pulmonary capillaries to the right heart and inferior vena cava. Pressure differences between the right or left heart are immediately transmitted to the contralateral side.

In the closed chest animal with experimental ventricular fibrillation, the heart and lungs function as a common vascular chamber, permitting retrograde circulation.

Reversal of the Cardiotoxic Effects of Quinidine and Procaine Amide by Molar Sodium Lactate

Samuel Bellet, Guillermo Hamdan, Andrew Somlyo, and Robert Lara, Philadelphia, Pa.*

The administration of molar sodium lactate to a patient resulted in a reversal of the cardiotoxic effects with quinidine toxicity. Because of the beneficial effects of molar sodium lactate in hyperkalemia and the similarity of the electrocardiographic effects of quinidine toxicity, the following studies were performed:

Quinidine gluconate was administered to 5 dogs at a rate of 1 mg. per Kg. per min. and the following studies were obtained: continuous electrocardiogram and blood pressure recording, quinidine levels, pH and serum electrolytes (potassium, sodium, magnesium calcium and chloride). These studies showed a gradual and constant progression in the severity of the electrocardiographic findings and a fall in blood pressure as the quinidine levels increased. Death of the animal occurred with a slow idioventricular rhythm.

These studies were repeated in 10 dogs following the administration of molar sodium lactate during various stages of quinidine cardiotoxicity. Following the infusion of molar sodium lactate, there resulted an almost immediate reversal of the cardiotoxic effects as manifested by a decrease in QRS widening and an increase in blood pressure. This was accompanied by a decrease in the quinidine plasma concentration, increase in pH, decrease in serum potassium and an increase in serum sodium. Similar results were obtained 2 or 3 times in the same animal.

Similar studies performed with procaine amide yield results that were similar to those obtained with quinidine. However, the reversal of cardiotoxic effects was even more striking and was observed at more advanced stages of toxicity than that observed with quinidine.

These studies would appear to have a bearing on the therapy of quinidine and procaine amide toxicity.

Phonocardiography in Pulmonary Stenosis

Alberto Benchimol and E. Grey Dimond, Kansas City, Kans.

A phonocardiographic study was made in 30 patients with pulmonary stenosis proved by cardiac catheterization.

First heart sound was normal in 21 cases, split in 1, accentuated in 4. In 3 cases in which first heart sound was accentuated, interatrial communication was present.

Fourth sound recorded in 12 cases; in 10 cases (83 per cent) RV pressure was above 90 mm. of mercury.

Systolic ejection sound was recorded in 8 cases. The distance of systolic sound from mitral component of first sound kept a good relationship with pressure in RV. The higher the pressure in RV, the closer the ejection click to first sound.

Correlation between duration of RV systole with RV pressure was attempted. Whenever pressure in RV was above 60 mm. Hg, a prolongation of RV systole above 0.31 seconds was found. In patients with pressure in RV above 90 mm. Hg, a right heart systole above 0.36 seconds was found. In 9 cases, the RV work could be determined; 7 cases revealed a prolongation of RV systole above 0.31 seconds.

A good correlation between duration of the splitting second sound at the pulmonic area and pressure in RV was found. In cases in which the distance between A2-P2 was greater then 0.6 seconds, pressure in RV was higher then 70 mm. Hg. A good correlation between duration of split second sound at pulmonic area with height of R wave in V_{4R} and VI in EKG was found. If R wave is higher then 6 mm., duration of splitting is greater then 0.07 seconds. In 7 patients in whom RV work was greater then 1.7 Kg. per M., duration of split was more then 0.65 seconds.

Electrocardiographic Criteria for Ventricular Septal Defect

Sheldon R. Bender, Leonard S. Dreifus, Daniel Downing, and Harry Goldberg, Philadelphia, Pa.

This study attempted to correlate the hemodynamic findings and electrocardiographic alterations in 100 cases of proven ventricular septal defect.

The material was further analyzed in an attempt to establish electrocardiographic criteria for the diagnosis of ventricular septal defect.

QRS—V_1 configuration showed RS (34 per cent), rR (10 per cent), rSR′ (9 per cent), R (6 per cent), qRs (6 per cent), qR (5 per cent), rS (3 per cent).

Of the various criteria suggested in VSD, right heart strain was seen in (70 per cent), R/S (ratio > 1) V_1 and V_6 (58 per cent), qRs associated with a positive T wave (47 per cent), large diphasic complexes in 2 of 3 limb leads (22 per cent), deep qV_6 (18 per cent), left axis deviation (18 per cent) diastolic type T waves (6 per cent), left ventricular hypertrophy alone (3 per cent) and left plus right ventricular hypertrophy (5 per cent).

Normal electrocardiograms were seen in all ranges of right ventricular pressure. Fourteen cases failed to meet any of the above criteria, while only 11 cases met all 8 criteria. In another 33 cases, 1 or more of these criteria were seen and the electrocardiogram was at best only suggestive of VSD.

Tall R waves V_1 and V_6 were frequently seen in ASD, PS, and PDA. Furthermore left ventricular hypertrophy was never noted either in the surgical or necropsy material. Hence, the electrocardiographic diagnosis of combined hypertrophy is untenable.

Although normal electrocardiograms were most frequently seen in the group with normal right ventricular pressures, no predominant electrocardiographic patterns were seen in any of the pressure ranges.

The failure to establish confident electrocardiographic criteria in VSD is not unexpected in view of the variable hemodynamic alterations as seen in this anomaly.

Pitfalls in the Diagnosis of Interatrial Septal Defects

Sheldon R. Bender, Joseph F. Uricchio, and Harry Goldberg, Philadelphia, Pa.

The purpose of this study is to evaluate the accuracy of criteria for the diagnosis of septum primum defects. The history, examination, x-rays, electrocardiograms, cardiac catheterizations, and radiopaque studies of 40 patients with diagnoses of interatrial septal defects were analyzed. Adequate surgical exploration was performed in all. Final diagnoses included septum primum, septum secundum alone or complicated by mitral insufficiency or interventricular septal defect, and atrioventricularis communis.

No marked differences in historical data were offered by patients with septum primum or secundum.

Apical systolic murmurs were most frequently observed in patients with the primum defect. However, when septum secundum was accompanied by mitral insufficiency, similar auscultatory events were noted. Left axis deviation was observed in only 2 of 16 patients with septum primum. It likewise was observed in all patients with septum secundum and associated mitral insufficiency.

Left ventricular hypertrophy was noted whenever mitral insufficiency was present, regardless of the type of defect.

Cardiac catheterization was of no value in differentiating the interatrial lesion either by chamber sampling or by positions of catheter.

Specialized radiopaque studies, including ventriculography, could not differentiate the primum from the secundum or atrioventricularis communis when mitral insufficiency was a complication.

In conclusion, there were no secure diagnostic methods by which the septum primum could be categorically differentiated from the septum secundum or atrioventricularis communis when the latter lesions were complicated by mitral insufficiency.

Left Atrial and Ventricular Pressure Pulses in Mitral Valve Diseases and in Subjects with Normal Mitral Valve

Jesus A. Bendezú, Chicago, Ill. and Chi K. Liu, Los Angeles, Calif.

Left atrial and ventricular pressure tracings, recorded in 6 subjects with normal mitral valve and in 24 patients with mitral valve disease by transthoracic puncture of the left atrium, were subjected to analysis.

The mean diastolic pressure gradient across the mitral valve has been considered evidence of mitral block, regardless of flow. The use of a stenosis index, obtained by the square root of the diastolic pressure gradient, is now proposed.

An elevation of mean left atrial pressure during ventricular systole above atrial diastolic pressure indicated insufficiency of the mitral valve. However, in the presence of severe mitral stenosis with a stenosis index above 3.16, the "insufficiency index" is not proportional to the amount of regurgitation because of greater tension of the atrial walls. On the other hand, even a slight increase of mean left atrial pressure during ventricular systole is evidence of significant mitral regurgitation if the stenosis index is below 3.16 because the atrial walls absorb, with their distension, part of the energy of the regurgitant jet.

The findings of Owen and Wood correlate well with present calculations in patients with predominant or pure mitral stenosis or insufficiency. On the contrary, no significant advantage is offered

by the method of Morrow et al. It is unfortunate that in the presence of significant mitral stenosis, a quantitative estimation of insufficiency can not be exactly determined by methods based on pressure tracings of the left heart.

A modified formula for the calculation of mitral valvular resistance is proposed.

Disposable Screen Oxygenator for Medical Use

Bernard A. Bercu, Gerald A. Diettert, William H. Danforth, and Ernest E. Pund, Jr., St. Louis, Mo.

A vertical screen oxygenator, with disposable screens and case, has been designed specifically for medical conditions. The unit employs one Sigmamotor pump as a dual arterial-venous pump and another as a recirculation pump. It has an oxygenating capacity of 1,500 ml. per minute and needs only 700 ml. of blood for priming. Either fresh heparinized or citrated banked blood with added heparin may be used. The entire unit may be autoclaved and kept ready for emergency use.

Venous return is obtained by gravity flow via a tributary of the femoral vein and oxygenated blood is returned retrograde into a convenient peripheral artery, usually the superficial femoral artery. In this manner part of the circulatory load is taken over by the pump oxygenator, resulting in a decreased work load for the heart.

The apparatus was tested in a series of dogs, some normal, and some in acute cardiogenic shock produced by intracoronary artery injection of lucite beads. The animals' own cardiac outputs were lowered 20-27 per cent in most instances by the effect of the pump-oxygenator. Left ventricular work fell up to 67 per cent during the perfusion.

This apparatus is now being applied clinically in cases of severe shock due to myocardial infarction, acute and chronic cor pulmonale, and chronic congestive heart failure. It might also be used in postoperative shock and total body perfusion with hypothermia.

Dye Dilution Curves in Mitral Valve Disease

Bernard A. Bercu, Gerald A. Diettert, Ernest E. Pund, Jr., and William H. Danforth, St. Louis, Mo.

Dye dilution curves, using Evans blue dye, were studied in patients with mitral valve disease to determine if those with predominant stenosis could be separated from those with predominant insufficiency. Approximately 4 ml. of the dye was injected via a cardiac catheter into the main pulmonary artery. The brachial artery was cannulated with a small polyethylene catheter. The arterial blood was drawn through a densitometer with a motor driven syringe for the recording of the dye dilution curve.

No attempt was made to quantitate the area or the height of the curve, but rather to compare various components of the curve. The appearance time (Ta) was measured as the time from the injection of the dye until the upstroke of the dye curve. The curve time (Tc) was considered as the time between the ascending and descending limbs of the curve extrapolated to the baseline. The least concentration of dye after the initial curve (CL) and the maximum recirculation concentration (CR) were measured as the heights of these points.

Forty patients were selected for study. The Tc minus Ta time varied from zero to 12 seconds in patients with predominant mitral stenosis and was always over 14 seconds in those with predominant mitral insufficiency. There was no overlap of the 2 groups by this test. The CL/CR ratio separated these 2 groups of patients in almost every instance.

It is concluded that right heart catheterization with dye curves is the method of choice for the study of mitral valve disease.

Effects of Unsaturated Fatty Acids on the Radioactive Fat Tolerance Test

Donald Berkowitz, William Likoff, and David M. Sklaroff, Philadelphia, Pa.

Recent studies have reported that unsaturated fatty acids (UFA) may reduce serum cholesterol and other lipids. Changes in the α/β lipoprotein ratio have also been observed following treatment with these preparations.

It would appear to be of greater fundamental importance to know whether UFA can effect more basic metabolic changes, specifically the reversion of abnormal fat tolerance to normal.

For this purpose, 25 patients with abnormal radioactive fat tolerance tests were studied. Twenty had evidence of coronary atherosclerosis. In 10 of these the cholesterol level was elevated. The remaining 5 patients had hypercholesterolemia but no findings of cardiac disease. Each was treated with a preparation of a soy bean oil emulsion containing 82 per cent UFA for a period of 4 to 8 months. The amount given was 45 ml. daily in divided doses before each meal. The diet remained normal with no restriction of fat or cholesterol-containing food.

A radioactive fat test meal containing 25 μc. of I^{131}-triolein was given at 2-3 month intervals during the course of treatment. The blood absorption patterns obtained were compared to the control studies.

In no case was there any improvement in fat tolerance noted. Peak blood radioactivity levels remained consistently higher than normal, as well a

the 24-hour values. Abnormal ratios of organic to organic blood radioactivity likewise were not altered. The results showed no relation to any decrease in the serum cholesterol that occurred in some patients, even if a normal level was eventually attained.

These studies indicate that although UFA may lower serum cholesterol levels, they do not exert an apparent effect on fat tolerance.

Cardiac Amyloidosis, Electrocardiographic Findings

Michael Bernreiter, Kansas City, Mo.

The object of this report is to describe the clinical pathologic and electrocardiographic findings in cases of amyloidosis of the heart muscle. The outstanding clinical finding was intractable heart failure, which only partially and temporarily responded to routine treatment. The electrocardiogram, while not specific, gave a suggestive pattern in all cases and was quite helpful in leading to the final correct diagnosis. In the presence of low QRS voltage in the extremity leads, complete or almost complete inversion of the QRS complexes in the first 3 or 4 precordial leads, one should consider the possibility of cardiac amyloidosis. This pattern gains in importance if a rhythmic disturbance, such as atrial fibrillation and conduction disturbances, are present. The electric alternation of the P waves was an interesting and unusual finding in one of our cases.

Shortness of breath on exertion was one of the first symptoms which brought the patient to his physician. Accumulation of fluid in the legs and abdomen occurred in all cases in the terminal stage of the disease. The final diagnosis was established by tissue biopsy or postmortem findings. In all cases, the condition is uniformly fatal with a survival time of about 4 years after beginning of symptoms. Extensive deposition of amyloid in the heart muscle was found in all our cases who came to autopsy.

Stokes-Adams Disease in Old Age

Kurt Biss, De Kalb, Ill., and Maurice Lev, Chicago, Ill.

One of us (KB) has studied 4 cases of Stokes-Adams disease in people over the age of 60. They all presented an identical clinical and pathological picture. There was no history, or evidence on physical examination of congenital cardiac defects, valvular disease, myocarditis or coronary artery disease. The presenting symptoms were syncope or convulsions. The electrocardiograms showed varying degrees of A-V blocks, and during the attacks ventricular tachycardia or fibrillation was observed.

At autopsy all 4 cases showed only minimal narrowing of the coronary arteries and no myocardial infarction. The outstanding feature was a marked thickening in the region of the base of the aortic leaflet of the mitral valve, extending into the membranous portion of the interventricular septum. In 1 case there was calcification within the lesion.

Detailed histologic studies of the conduction system were done in 1 case by 1 of us (ML). This revealed fibrosis and calcification at the summit of the ventricular septum with scar formation at the junction of the bundle of His and the right and left bundle branches. The conduction system of a second case is now being studied.

A review of the literature reveals that this type of Stokes-Adams disease was last comprehensively studied by Yater in 1935, but has been neglected in recent years. It is the purpose of this paper to reemphasize the frequency and the importance of this type of Stokes-Adams disease seen after the age of fifty.

Calcification of the Coronary Arteries

David H. Blankenhorn, Los Angeles, Calif.

At present, the clinical diagnosis of coronary atherosclerosis depends upon recognition of some manifestation of impaired myocardial blood supply. More direct diagnostic technics yielding information as to the size, character, and location of coronary lesions are needed. Coronary arteriography can provide such information, but entails sufficient hazard and labor that it does not appear applicable to routine use. Calcification in the coronary arteries can be visualized by x-ray. This technic, previously proposed by others, entails no risk and can be made routine.

A study has been performed to determine what calcific lesions occur in human coronary arteries and what might be learned if these calcifications were recognized during life. Postmortem x-ray of 80 hearts from unselected patients 17-95 years of age indicates that: coronary calcification can be differentiated from other intracardiac calcification by location and appearance; coronary calcification occurs only in atheromatous lesions; a calcific plaque 5 mm. or more long occurs in 40 per cent of hearts (32 of 80).

Present-day x-ray technic allows consistent recognition of solitary lung nodules which exceed 3 mm. If improved x-ray technic could effect comparable recognition of coronary calcification, exact information regarding coronary atherosclerosis would become available to the clinician in up to 40 per cent of adults.

Quantitation of Valvular Insufficiency by a Continuous Infusion Indicator Dilution Technic

Harry A. Bliss, Irving J. Adatto, William J. Grove, and William R. Best, Chicago, Ill.

When an indicator is injected into the left ventricle at a constant rate for several minutes, brachial arterial and left atrial blood concentrations soon rise at approximately parallel rates. Cardiac output equals the quantity of indicator injected per minute divided by the instantaneous brachial arterial-left atrial concentration difference corrected for mean transit time between the two points (Method 1).

In the presence of mitral insufficiency, this concentration difference decreases and apparent cardiac output by Method 1 increases. If one then measures effective cardiac output by instantaneous indicator injection into the left atrium with brachial arterial sampling (Method 2), it can be demonstrated that mitral regurgitant flow per minute equals the difference between the flows determined by Method 1 and Method 2. Aortic valvular insufficient flow can similarly be determined if one continuously injects indicator into the immediately supravalvular aorta and samples from the brachial artery and left ventricle. If uniform mixing of regurgitated indicator in the upstream chamber is assumed, the technic is valid and not influenced by the blood volume in cardiac chambers or aorta.

This approach was used to quantitate insufficiency of the aortic valve in 3 patients and of the mitral valve in 2 patients. The data obtained agreed well with clinical and operative estimates of insufficient flow in all but 1 instance where it was somewhat higher than expected.

This method is less affected by transient flow variations than instantaneous injection methods. The assumption of homogeneous upstream mixing of regurgitated indicator is being investigated in dogs.

Diagnostic Use of I^{131}-Diodrast in Hypertension due to Unilateral Renal Disease

Jerome B. Block and Belton A. Burrows, Boston, Mass.

The use of I^{131}-labeled Diodrast, with external monitoring over the renal areas, as a screening procedure for unilateral renal disease, has been compared in 22 hypertensive patients with the results of intravenous pyelography (IVP), the Howard Test, and differential I^{131}-Diodrast excretion. The method entails directing a scintillation counter at each kidney, intravenous administration of I^{131}-Diodrast with "carrier" Diodrast. Changes in radioactivity of a single kidney and the ratio of radioactivities of both kidneys are directly recorded. Abnormal tests consist of either diminished uptake of I^{131}-Diodrast by 1 kidney without a difference between the kidneys in the rate of excretion (Type I), or diminished uptake and delayed excretion of I^{131}-Diodrast by 1 kidney relative to the other (Type II).

Six patients with surgically proved unilateral renal disease all showed abnormal I^{131}-Diodrast tests, Type II in four and Type I in two. Two of these patients had positive Howard tests, with normal IVP's. Three others had unsatisfactory Howard tests with abnormal IVP's.

Thirteen patients had negative Howard tests and IVP's. Nine of these had negative I^{131}-Diodrast tests, 2 had Type II tests and two, Type I. Ureteral catheterization showed a difference in I^{131}-Diodrast excretion in the latter patients; similar data were not available in the Type II cases. Three additional patients with negative I^{131}-Diodrast tests and IVP's were shown by biopsy or autopsy to have no anatomic differences between the kidneys.

Hence, the results of I^{131}-Diodrast studies correlated well with ureteral catheterization studies, less well with IVP's in patients studied for unilateral renal disease.

Marfan's Syndrome and the Weill-Marchesani Syndrome in the S. Family

Dorrance Bowers, Kelowna, B. C., Canada

At least 33 members (17 of whom are now dead) in 6 generations of the S. family have displayed the characteristics of Marfan's syndrome (31 cases), or of the Weill-Marchesani syndrome (2 cases). The incidences of the stigmata of Marfan's syndrome in the 17 affected members known to have been examined by physicians or optometrists were: dislocation of ocular lenses in 94 per cent of cases; dolichocephaly in 94 per cent; arachnodactyly in 74 per cent; and clinical evidence of aortic disease in 15 per cent. The incidences of these stigmata did not change appreciably from one generation to the next in the medically-examined affected members of the fourth, fifth, and sixth generations. Affected male members now dead had a lower fertility rate (average 0.4 children each) and a lesser capacity to transmit the abnormal gene (average 0.1 affected children each) than did affected female members (average 4.7 children each; average 2.3 affected children each). The average lifespan of 16 deceased affected members was 45 years. Cardiovascular diseases caused the deaths of at least 11 of 17 affected members; aortic disease accounted for at least 3 of the 11 deaths attributed to cardiovascular diseases.

These observations support the conclusions that, in this family, Marfan's syndrome and the Weill-

Marchesani syndrome are transmitted by a single pleiotropic abnormal gene; expression of this gene results in an abiotrophy of the cardiovascular system and prohibition of child-bearing by affected females would reduce the number of affected individuals in succeeding generations.

Heart Disease in Friedreich's Ataxia: Incidence and Manifestations

Samuel H. Boyer, Victor A. McKusick, and Arthur W. Chisholm, Baltimore, Md.

Friedreich's ataxia, a rare heritable spinocerebellar degeneration, is often accompanied by heart disease. Evans and Wright observed electrocardiographic abnormalities in 12 of 38 patients. Our experience suggested a considerably greater incidence of cardiac disturbance and a survey was consequently made of all patients (33) with Friedreich's ataxia seen at the Johns Hopkins Hospital from 1935 to 1957. Electrocardiograms were obtained from 31 and chest x-rays from 29 of these individuals. In all cases the patient's present condition was determined.

Eighteen persons exhibited 1 or more signs of heart disease. Cardiac enlargement occurred in 5, angiocardiographic evidence of pericardial effusion in 1, loud systolic murmurs in 6, and a presystolic murmur in 1. Prominent electrocardiographic abnormalities appearing in 17 patients included left precordial T-wave inversion in 14, multiple ectopic beats in 4, and atrial fibrillation or flutter in 3. An unusual feature of serial recordings was the partial or complete disappearance of T wave abnormalities in 4 individuals. Eight patients died. Arrhythmias or congestive heart failure was a contributory cause of death in 5. Autopsy was performed in 1 person with heart disease. There was extensive myocardial fibrosis without inflammation. Valves were normal and coronary arteries patent.

Eight patients masqueraded as congenital or rheumatic heart disease. Rheumatic fever was often closely simulated by the early appearance of murmurs and leg pains.

Known causes of heart disease were absent in all patients, suggesting that both neurologic and cardiac disturbances resulted from a single genetic fault.

Second Heart Sound in Atrial Septal Defect

Samuel H. Boyer and Arthur W. Chisholm, Baltimore, Md.

Early occurrence of the aortic closure component contributes equally with delay of the pulmonary closure component to the normal increased inspiratory splitting of the second heart sound. Fixed splitting in cases of atrial septal defect has been assumed to appear when respiratory changes no longer alter the already increased right ventricular stroke volume. In 11 cases of known atrial septal defect, it was possible to time the second sound components with an accuracy of 3 msec. through at least 3 normal respiratory cycles. In every case, the aortic component was fixed or moved paradoxically, whereas the pulmonic component showed the usual phasic respiratory movement within the range for normals.

It is concluded that the engorged pulmonary vascular bed fails to respond to respiratory changes. Fixation of left ventricular stroke volume and aortic closure sound occur. Paradoxic movement of this sound may be due to unusual pressure volume characteristics of an overloaded pulmonary circulation or to a reflection of right atriocaval respiratory events in the left atrium. The demonstration of fixation of the aortic closure sound is suggested as a sign of pulmonary vascular engorgement and paradoxic movement of this sound as a sign of atrial septal defect. In 2 recent cases, large pulmonary arteries and wide second sound splitting with pulmonary systolic murmur clinically suggested atrial septal defect. Normal aortic closure sound movement correctly predicted that no defect would be found.

Clinical Application of the K-Agar Test for Serum β Lipoproteins and Cholesterol in an Epidemiologic Survey

Edwin Boyle, Jr.,† and Robert V. Moore, Charleston, S. C.

In a study of 4 generations of familial hypercholesterolemia, ultracentrifuge lipoprotein fractionation, total cholesterol, and K-Agar values were determined. The results of this new K-Agar β-lipoprotein precipitation method were compared with data obtained by differential density floatation of serum β-lipoproteins, with subsequent chemical analysis of cholesterol content of the fractions, and with the total serum cholesterols.

The K-Agar test consists of the addition of 3 ml. of buffered K-Agar (pH 6.8) solution to 0.2 ml. of serum and reading the resulting optical density at 540 mu. in a colorimeter. In 150 subjects studied, the following correlations were made: K-Agar values in optical density units $\times$ 1,000 = 1.607 $\times$ cholesterol (mg. per cent) – 38. The correlation coefficient r = .986. Standard deviation from regression line = .037 O. D. units. In correlating K-Agar values to serum beta lipoprotein cholesterol content, K-Agar (O. D. units) $\times$ 1,000 = 1.953 $\times$ cholesterol (mg. per cent) + 7. The correlation coefficient = .986, with standard deviation of .0286 O. D. units. Similar correla-

tions on serum samples of 500 factory employees gave essentially the same values. This test, costing less than 1 cent each for the materials, and 2 minutes time to complete, provides a reliable, accurate means of estimating serum cholesterol and β-lipoprotein levels at epidemiologic proportions.

Experimental Approach to the Study of the Electrocardiographic Changes of Acute Cor Pulmonale in Man

Jonas Brachfeld, David H. Lewis,† and Santiago V. Guzman, Philadelphia, Pa.*

Candidates for lung surgery were evaluated by unilateral pulmonary artery occlusion. In 24 cases complete hemodynamic observations and electrocardiogram (including V_{3R} and V_{1R} before and during occlusion were obtained. Marking the chest insured reproducibility of the precordial leads.

Others have reported no change in the electrocardiogram during such occlusions. This was seen in 6 cases. However, electrocardiographic changes occurred in 18 cases. Most commonly, there was a diminution of the T wave in the left precordial leads. In some there was an increase in the T wave in the right precordial leads, either reciprocally or independently. Decreases in the QRS in the left and midprecordial leads with or without reciprocal changes in the right precordial leads were also seen. Alterations in the S-T segment were not observed. In two cases there was a rightward shift of the P axis.

While unilateral pulmonary artery occlusion has proven to be a valuable and safe method for evaluating pulmonary vascular reserve, it also provides an opportunity for studying the effect on the electrocardiogram of hemodynamic alterations of the lesser circulation, particularly pulmonary embolism. Simple mechanical obstruction of the pulmonary bed reproduces neither the clinical picture nor the electrocardiographic changes seen in pulmonary embolism. Moreover, repeated observations by us failed to confirm the isolated observation of Brofman, et al., that peripheral occlusion produces the changes seen in pulmonary embolism. Finally, in one case, to be discussed in detail, pulmonary artery occlusion was well tolerated despite a recent episode of acute cor pulmonale precipitation by pulmonary embolism.

Physiological Evaluation of Chest Pain

Norman Brachfeld, Joseph Messer, John Turner, and Richard Gorlin, Boston, Mass.

Electrocardiographic and ballistocardiographic evaluation of chest pain is primarily a measure of myocardial dysfunction from coronary insufficiency rather than an evaluation of coronary flow itself. Measurement of coronary flow (N_2O method) and coronary vascular resistance (CVR) before and after nitroglycerin induced vasodilatation has been accomplished by the technic of coronary sinus catheterization. In normals, coronary flow per 100 Gm. muscle increased an average of 63 per cent with a fall in CVR of 42 per cent. Simultaneous left ventricular O_2 consumption, systemic arterial pressures, heart rate and output were also determined.

Fifteen patients with angina pectoris, due either to aortic valvular disease or coronary artery disease, were studied. They showed a positive exercise two-step test or EKG evidence of coronary insufficiency, or of old myocardial infarction at rest. Coronary flow and O_2 consumption per 100 Gm. (normal at rest) fell or were unchanged while CVR ($\pm$ 10 per cent) remained fixed after nitroglycerin. Left ventricular work and efficiency fell precipitously in these patients after nitroglycerin.

A second group presenting symptoms of chest pain but failing to show EKG evidence of coronary insufficiency was evaluated before and after a challenging dose of nitroglycerin. Both normal and abnormal coronary flow responses were found in this group. A finding of fixed coronary flow in some and coronary vasodilatation in others helped in the differential diagnosis of pain resulting from true coronary insufficiency and that due to other causes.

This difference in the relative reactivity of the coronary circulation affords a physiologic method of demonstrating exhaustion of coronary vascular reserve.

Observations on the Natural History of Patients With Atrial Septal Defect

Robert O. Brandenburg, H. J. C. Swan, Jesse E. Edwards, and John W. Kirklin, Rochester, Minn.

In the past 5 years, atrial septal defect has been diagnosed in about 300 patients. This figure excludes total anomalous pulmonary venous drainage, defects of the atrioventricular canal and atrial defects with other cardiac lesions. About 200 of these patients have undergone surgical repair of the defect. When operation was not done, the reasons therefore were: (1) severe pulmonary vascular resistance with pulmonary blood flow less than systemic flow; (2) older patients with small defects and minimal, if any, symptoms; (3) the presence of other complicating medical illnesses; and (4) patient elected not to have surgical treatment. Patients treated surgically ranged from children to persons in the seventh decade.

The data indicate that serious pulmonary hypertension is unusual in childhood. The data also indicate that older patients may have a persistent moderate left-to-right shunt with only mild or moderate pulmonary hypertension. However, in certain young adults, particularly women, severe pulmonary vascular obstructive changes may develop in a short period.

Most of the group had moderate to large left-to-right shunts, without significant elevation of pulmonary arterial pressure. Smaller groups had: (1) significant left-to-right shunts in the presence of severe pulmonary hypertension, (2) balanced bidirectional shunts with essentially equal systemic and pulmonary arterial pressures; and (3) predominant right-to-left shunt associated with severe obstructive pulmonary vascular disease. Congestive heart failure was present in small numbers in each category of patients.

Hemodynamic Features in Congenital Aortic Stenosis and Their Modification by Operation

Eugene Braunwald and Andrew G. Morrow, Bethesda, Md.

Twenty-eight patients with congenital aortic stenosis were studied by catheterization of both sides of the heart. Left ventricular pressure was measured by the transbronchial methods (19 patients) or by direct ventricular puncture (9 patients). Aortic valve gradients ranged from 15 to 172 mm. Hg, averaging 82 mm. Hg. Left ventricular end-diastolic pressures ranged from 2 to 28 mm. Hg, exceeding 15 mm. Hg in 8 patients. Effective orifice size, measured in 8 patients, ranged from 0.2 to 1.1 cm.^{2} per M.^{2} B.S.A. Pulmonary capillary wedge pressure was elevated above 12 mm. Hg in 6 patients. Significant pulmonary arterial hypertension was present in only 1 patient. In 2 of the 8 patients with associated aortic regurgitation, the regurgitant flow measured by a dye-dilution method averaged 1.5 L. per minute.

With one exception, the resting cardiac indices were within normal limits. No correlation existed between the aortic valve gradient and the resting cardiac index. The site of stenosis could not be localized by clinical or angiocardiographic technics. However, the demonstration of an intermediate pressure zone between left ventricle and aorta proved subvalvular obstruction, while absence of this zone indicated valvular stenosis.

Currently, operation is carried out if the aortic valve gradient exceeds 60 mm. Hg, or the estimated orifice size is less than 0.5 cm.^{2} per M.^{2} B.S.A. Postoperative studies were performed in 13 of 17 operated patients. The aortic valve gradient was reduced in all patients and was completely abolished in 3. The gradient fell by an average of 75 mm. Hg.

Three-Dimensional Statistical Technic: Its Application to the Ventricular Gradient

Louis Brinberg, New York, N. Y.

The gradients of 49 normal subjects are represented by their vector termini, which form a cluster of points in space. The mean gradient lies at the center of this cluster and is the null-point of concentric spheres whose radii are expressed in standard deviation units. The deviate of a gradient is its distance in microvolt-seconds from the mean gradient. Its cartesian coordinates are obtained by subtracting those of the latter from those of the former. Its spherical coordinates relative to the mean gradient are then determined on a chart. From a mean gradient whose coordinates are 54 μs., 23°, 38°, (magnitude, azimuth, elevation), as extracted from the 12-lead electrocardiogram, the mean deviation is 25 μs., the standard deviation 27 μs. The range is 6 to 68 μs. Thirty-one gradients lie within a sphere whose radius is 1 S.D., 48 within 1 of 2 S.D., and 49 within 1 of 3 S.D. The frame of reference of the mean gradient gives azimuth a range of 0° to 180° as measured from the subject's left. The anterior hemisphere is positive; the posterior, negative. Elevation ranges from 0° to 90°. The lower hemisphere is positive; the upper negative.

Relative Merits of the Proximity Lead and Equivalent Cardiac Dipole Concepts of Precordial Electrocardiograms

Daniel A. Brody and G. Daniel Copeland, Memphis, Tenn.

Impressive evidence has recently been presented that Wilson's semi-direct lead concept of precordial electrocardiograms can be supplanted by simple representation of the heart as a single dipolar generator of fixed location and variable moment. In an attempt to evaluate the relative merits of these 2 essentially contradictory concepts, we report here a study of ventricular depolarization in 17 normal subjects in whom lead aVr was compared with numerous apical precordial electrocardiograms by means of an improved cancellation technic. Two general features emerging from this study cast some doubt on the ultimate accuracy of the equivalent cardiac dipole: (a) excellent peak-to-peak cancellations occurred over significantly extensive areas of the apical precordium; (b) instant-by-instant analysis showed poor cancellation occurring during numerous subintervals of QRS inscription. Ordinary cancellations are probably unreliable indicators of dipolar behavior because of the virtual certainty that exact cancellation will occur at least twice during ventricular depolariza-

tion despite significant translocation of the electrical center, and because residual cancellation potentials tend to be relatively small during most other instants of QRS inscription.

Although the equivalent dipole approximation in its modern form should eventually attain considerable clinical utility, it appears that the Wilson concept of proximity leads may be significantly more accurate. Accordingly, pending indisputable proof that electro- and/or vectorcardiographic lead systems based on the dipole approximation can provide all available diagnostic information, the current practice of multiple precordial electrocardiographic registration should be continued.

Collateral Circulation in Coronary Heart Disease: "Benign" or "Malignant"?

Bernard L. Brofman, Cleveland, Ohio

Despite multiple coronary artery occlusions, the integrity of the myocardium can be maintained almost indefinitely as long as adequate collateral circulation provides uniform distribution via a final common pathway. Chronic occlusive disease is the stimulus, par excellence, in activation of intercoronary collaterals; however, in view of the exorbitant mortality of this disease, it is unrealistic to assume that all patients with clinical manifestations of coronary heart disease are developing adequate "natural" protection.

A large series of patients undergoing the Beck operation for coronary heart disease provided a unique opportunity for *direct* hemodynamic and metabolic observations on such hearts. Direct sampling of blood from the coronary sinus (or suitable coronary vein) permitted serial determinations of the myocardial coefficient of extraction:

$$\left(\frac{\text{A-V}}{\text{A}}\right)$$

for oxygen and other substrates. Contrary to *a priori* reasoning, in patients with extensive myocardial scars, a *decrease* in oxygen extraction (*increased* coronary venous oxygen content) was frequently observed.

In an autopsied series of 100 patients who died following acute myocardial infarction, at least 15 deaths occurred at the thirteenth to fifteenth day, rather inexplicably, in that autopsy revealed no further "immediate" cause of death. It is apparently more than coincidental that by this time a well-developed collateral circulation has already been achieved.

Conclusion: Intercoronary communications *in advance* of the occlusive process are beneficial. The extensive collaterals resulting from coronary occlusion and myocardial infarction, in encouraging preferential perfusion of an inert scar at the expense of adjacent viable myocardium, may be deleterious.

Continuous Measurement of Thoracic-Aortic Flow During Head-Up Tilt in Man

Raymond E. Brow, Darryl K. Foerster, H. J. C. Swan, and Earl H. Wood, Rochester, Minn.

The technic of constant-dye infusion was used to study the rapid circulatory adjustments to sudden changes in posture by continuous measurement of aortic flow over a 60-second period punctuated by a 20-second interval in the 70°-tilt position. Right atrial, saphenous vein, aortic and radial artery pressures, electrocardiogram and respiration also were recorded. The reactions to tilting of 6 healthy physicians were studied under the following conditions: (1) control; (2) partial ganglionic blockade with 5 mg. of tetraethylammonium chloride (TEA) per Kg. of body weight; (3) pressurization of lower portion of body by an antiblackout suit; (4) continuous infusion of 9 μg. of levarterenol per second into the thoracic aorta.

Variations in aortic flow of ± 9 per cent occurred in the resting supine position. Tilt produced an average initial increase of questionable significance, followed by a gradual decrease to 80 per cent of the mean resting value. After administration of TEA, this pattern was exaggerated, the increase amounting to 20 per cent followed by a decrease to 20 per cent below control values. During pressurization, an increased flow was maintained during tilt, while infusion of levarterenol caused a progressive decline in flow which, after an initial increase, was maintained during tilt. Total vascular resistance in the lower portion of the body was inversely related to the aortic-flow pattern.

The autonomic nervous system apparently regulates distribution of blood flow in order to maintain a blood pressure which will assure an adequate cerebral circulation. By alternately blocking and stimulating this system, as well as redistributing blood by body pressurization, study of the effectiveness and mechanisms responsible for these rapid circulatory adjustments is facilitated.

Exertional Hypotension in Cardiac Patients

Robert A. Bruce, W. Wyman Andrus, Theodore J. Fuller, Leonard A. Cobb, Shigeaki Katsura, and John H. Morledge, Seattle, Wash.

Cardiac patients studied by clinical sphygmomanometer during exercise (walking) in the upright posture have exhibited atypical hypotensive responses. The incidence in 168 patients varied from about 16 per cent in persons with valvular regurgitation or left to right shunts to 44 per cent in

individuals with valvular stenosis. Hemodynamic mechanisms have been studied by catheterization of radial and pulmonary arteries for direct recording of blood pressure and determination of cardiac output by direct Fick principle during a steady state of lying supine, sitting and walking at 3.7 m.p.h. on a 10 per cent grade on a treadmill. Eighteen randomly selected cardiacs were mildly sedated and only 13 could be studied completely; also of 13 additional cases who were not sedated could be tested.

"Exertional hypotension," or a fall in mean systemic arterial pressure during walking as compared with sitting occurred in 10 patients (38 per cent). These patients had lower cardiac index and higher peripheral resistance while sitting, some increase in cardiac index due to acceleration of heart rate, and marked limitation of stroke index during walking. The other 16 patients demonstrated significantly greater changes in stroke index ($p < .003$) and cardiac index ($p < .02$) during exertion. There was a similar fall in peripheral resistance in both groups.

When there is neither a marked reduction in blood volume nor impairment of neural regulation of vasomotor tone, exertional hypotension is an important sign of impaired cardiac function.

General Theory of the Cause of Cardiovascular Murmurs

David L. Bruns, San Francisco, Calif.

The classic theory that murmurs are due to turbulence in flowing blood has been examined in the light of recent studies of aerodynamic noise. It is found that this theory is untenable.

It is postulated that murmurs arise from nearly periodic wake fluctuations generated by blood in a manner similar to the production of Aeolian tones.

Employing the Melrose extracorporal circulation pump, water and blood were propelled through plastic and thin-walled rubber tubes of a mass less than the aorta and large arteries. No noise was heard or recorded under fully turbulent flow (Reynolds number of 15,000).

On the other hand, Aeolian tones were generated by placing a straight or curved wire in the stream. The noise produced was similar to murmurs. If the tubing wall is abruptly narrowed, the same type of wake fluctuation is produced which again leads to the appearance of audible noise. Orifice flow, a special case of Aeolian tones, also produced detectable sound. These structures are physically similar to anatomic deformities which are known to produce murmurs. Velocities of flow and the frequencies of the murmurs were within the range of those occurring in the body.

Atrial Electrocardiographic Activity

Cesar A. Caceres and George A. Kelser, Jr., Washington, D. C.

Left and right atrial intracardiac and conventional surface leads were used to study electrocardiographic activity during the PR interval. Electronic filters were employed for analysis of wave frequency and harmonic content from 0.1 to 2,000 c.p.s. Amplifiers permitting standardization sensitivities to 500 mm. per mv. were used to obtain oscilloscopic tracings recorded at a paper speed of 75 mm. per second.

During the interval of the P-R segment, rapid electrical potential changes, not apparent in standard electrocardiograms, were detectable.

Simultaneous tracings of intracardiac and conventional leads, when recorded with appropriate standardization sensitivities, demonstrated that the PR segment duration was identical with concurrent onset and termination in all leads. Similarly, the P wave duration was identical with concurrent onset and termination in all leads.

Frequency analysis of the electrical potential recorded during P wave inscription demonstrated the presence of high frequency content that is excluded by conventional electrocardiographic amplifiers and recorders.

A spike of electrical activity of high intensity with a high frequency content was noted approximately 0.03 to 0.04 seconds after the onset of the P wave. Its occurrence after the initiation of atrial depolarization suggests that, during specific intervals of the cardiac cycle, portions of myocardial tissue are emitting or generating electrical activity of specific wave frequencies.

Possible Genetic Determinants of Congenital Heart Disease: Study of Familial Occurrence

Richard A. Carleton, Walter H. Abelmann,† and Ernest W. Hancock, Boston, Mass.*

Three families with multiple instances of congenital heart disease were found among 37 families with at least 1 such defect. The first family has 11 members: of 9 siblings 1 has an atrial septal defect and another has coarctation of the aorta with probable bicuspid aortic valve. The second family contains 30 members with 2 of 5 siblings and the daughter of 1 sibling afflicted with atrial septal defect. The third family has 72 members: 3 of 16 siblings have atrial septal defect and the daughter of 1 patient has a ventricular septal defect with pulmonic stenosis.

These families have a 7.9 per cent (9 of 113) incidence of congenital heart disease. This frequency of affected persons made a search for possible etiologic factors mandatory. A careful re-

iew of the gestational histories of these 9 patients failed to reveal any environmental cause. A genetic analysis disclosed that 7 of 30 members of the first affected sibships have congenital heart disease. The ratio of males to females in these first involved sibships is 1 : 1.2, and of the affected members is 1 : 8. Those families with at least 1 descendent of a propositus affected have a second generation ratio of 2 affected : 3 unaffected.

These facts are consistent with the hypothesis that a single, autosomal, recessive gene has determined the frequent occurrence of congenital heart disease in these families, and that second generation occurrence represents a heterozygous mate of the propositus.

Effect of the Valsalva Maneuver on Oxygen Saturation of Arterial and Central Venous Blood in Patients With Intracardiac Shunts

Stefan A. Carter, Newton C. Birkhead,° and Earl H. Wood, Rochester, Minn.

A decrease in arterial oxygen saturation after the Valsalva maneuver has been reported in patients with interatrial communication. We recorded continuously the oxygen saturation of arterial blood by earpiece and cuvette oximetry before, during and after the Valsalva maneuver (volutary elevation of airway pressure to 40 mm. Hg for 15 seconds). The saturation of blood withdrawn simultaneously from the pulmonary artery or other central sites was recorded continuously in these same maneuvers.

A sudden decrease in arterial saturation shortly after the maneuver was found in 8 of 11 patients with interatrial communications and in 4 patients with interventricular communications and right ventricular systolic hypertension. This was not observed in 10 subjects without shunts or in 2 patients with interventricular communications without marked elevation of right ventricular pressure. Comparison of pulmonary-vein and systemic-artery saturation changes during the Valsalva maneuver in patients with interatrial communications suggests that the decrease in arterial saturation after the maneuver is due to a temporary right-to-left shunt.

All patients with intracardiac shunts showed an increase in the pulmonary-artery saturation above the control level during the period of increased intrathoracic pressure, suggesting an increase in left-to-right shunt in relation to systemic venous return. This was not observed in patients without shunts.

These reactions may be of special diagnostic value under particular circumstances, but their detection by ear oximetry alone is not uniformly reliable.

Use of a Radioactive Gas in the Detection and Measurement of Circulatory Shunts

Robert B. Case, Paul Keating, H. L. Sachs, New York, N. Y.

Previous animal work by the above authors demonstrated that inhalation of ethyl iodide containing I^{131} was a safe, rapid and accurate way of detecting left-to-right shunts. The present work concerns the extension of this method to humans, and the eveluation of a proposed formula for the measurement of the shunt. Using simple mixing formulae before recirculation, it may be shown that:

$$\frac{Q_s}{Q_{pf}} = \frac{C_{pa}}{C_a}$$

Where

Q_s = amount of shunt flow

Q_{pf} = amount of pulmonary flow

C_{pa} = mean concentration of radioactivity in the pulmonary artery

C_a = mean concentration of radioactivity in the aorta

Radioactive ethyl iodode was administered to 5 patients with left-to-right shunts, and to 6 patients with no shunts. Mean concentrations of radioactivity were obtained by taking a single, 5 ml. integrated sample simultaneously from the brachial artery and the pulmonary artery, over a 20 second period following the inhalation of the radioactive gas. C_{pa}/C_a varied from 0 per cent to 5.0 per cent in the normals, averaging 2.0 per cent. In the shunt cases, C_{pa}/C_a varied from 29.2 per cent to 70.2 per cent, averaging 44.5 per cent. Thus there appeared to be a clear indication of the shunt in all cases. One advantage of this method is that the results are obtained within a few minutes, while the catheter is still in place.

Calculations of the size of the shunt by the traditional oxygen method and the ethyl iodide method using the above formula were in essential agreement.

Effect of Relaxin on Occlusive Peripheral Arteriosclerotic Disease

Gus G. Casten and Hugh R. Gilmore, III, Miami, Fla.

Previous reports from this laboratory demonstrate that relaxin, "the third hormone of pregnancy," exerts a beneficial effect on Raynaud's phenomena and ischemic ulceration in scleroderma. These results have prompted study of the effect of relaxin on 8 patients with arteriosclerosis obliterans.

Prior to relaxin therapy, the mean of 3 determinations of surface skin temperature under conditions of maximal vasodilation in 36 abnormal toes was 27.3 C. (range 24.5 C. to 29.7 C.). Continuous relaxin therapy (7.5 mg. to 20 mg. intramuscularly daily) was then begun, coupled with estrogen "priming" (Premarin, 1.25 mg. 3 times weekly). Skin temperature measurements, at intervals of 2 weeks to 1 month, revealed a progressive rise. After 3 months of therapy, the mean level had increased to 30.9 C. (range 27.2 C. to 35.0 C. ($p < 0.001$).

Every toe studied revealed an increase. After 4 months of therapy, all toes had reached a normal range of 30.0 C. or above. Those patients studied after 6 months of continuous therapy have maintained a normal range. Discontinuation of therapy is followed by return to pretreatment values.

Studies of blood flow to the calf muscles employing direct stimulation ergometry (Edwards-Murphy Ergometer) have been made in 3 patients. Increase of 2 times or more in ergometric "energy units" occurred after 3 months of therapy. Further increase (4 times control) has occurred after 5 months of therapy in 1 patient. This coincides with subjective improvement in all patients.

Relaxin exerts a known effect upon connective tissue and presumably alters collagen. Although the manner in which relaxin produces a striking increase in blood flow to the extremity is unknown, this hormone offers promise in the therapy of obliterative vascular disease.

Pre- and Postoperative Evaluation of Mitral Stenosis with the Maximal Oxygen Intake Test

Carleton B. Chapman, Jere H. Mitchell, and Brian J. Sproule, Dallas, Texas

Studies concerning factors which determine maximal oxygen intake in normal subjects suggest that the test may be useful in evaluating patients with mitral stenosis, and for objective appraisal of valvulotomy.

In 18 male patients with mitral stenosis, maximal oxygen intake was about half the normal expected value. Cardiac output during exercise sufficient to produce maximal oxygen intake in patients was double the resting value; in normal subjects it was about 4 times the resting value under comparable circumstances. Increase in cardiac output in the patients, unlike that in normal subjects, was achieved mainly by elevation of pulse rate, since stroke volume did not change. Appearance time (Evans blue) did not decrease in the mitral group during exercise; in normal subjects it was reduced by half.

In neither group did arterial oxygen tension (polarographic) decrease during exercise; the lowest femoral venous pO_2 in exercising patients was 8 mm. Hg.

Valvulotomy in 5 patients produced a slight increase in maximal oxygen intake (1.63 to 1.88 L. per minute) and in cardiac output (10.3 to 12.8 L. per minute); there was a greater increase, however, in stroke volume.

The data suggest that the hemodynamic effect of surgery, as judged by studies done 3 to 12 months after operation, is slight. They also suggest, however, that valvulotomy permits patients with mitral stenosis to adjust more efficiently to exercise than do unoperated patients. Finally, the data do not rule out the possibility that studies at longer periods after surgery will show still greater quantitative improvement.

Myocardial Aneurysms and Interventricular Septal Rupture Following Coronary Occlusion, Successfully Repaired Using Cardiopulmonary Bypass

Don W. Chapman and Denton A. Cooley, Houston, Texas

Myocardial aneurysms have been encountered in 10 patients, 4 of whom are still surviving. All were found to involve the left ventricle. Persistence of S-T segment elevation was noted in 4 and all revealed electrocardiographic evidence of previous myocardial infarction. Teleroentgenograms, laminograms and angiograms were used further to delineate their location. At 3 months postinfarction, 1 patient with persistent borderline cardiac failure had a successful surgical excision of a large left ventricular aneurysm employing the cardiopulmonary bypass. A second patient with a myocardial aneurysm was found to have a preoperative cardiac index of 1.6 L. and a right ventricular pressure of 60/5 mm. Hg. Postoperative cardiac indices revealed 1.84 L. resting, and with exercise 3.6 L., and a reduction in right ventricular pressure to 30/0 with rest and exercise. The high incidence of congestive failure, rhythm disturbances, and thromboembolic phenomena and shock in myocardial aneurysm should be reduced with this procedure.

On the fifth postmyocardial infarction day, an acute interventricular septal perforation was thought to have developed in a 51-year-old male, and persistent right-sided cardiac failure ensued. At the end of 9 weeks, right heart catheterization established the diagnosis, and a successful repair of the interventricular septal rupture was accomplished, using the cardiopulmonary bypass.

Cardiopulmonary bypass has provided a new surgical approach to 2 unusual complications of myocardial infarction, namely, myocardial aneurysm and rupture of the interventricular septum which has stabilized.

Electrocardiographic Correlation with Systolic Ventricular Pressure In Pulmonary Stenosis with an Intact Ventricular Septum

Don W. Chapman, K. Amad, and Denton A. Cooley, Houston, Texas

In 10 cases of pulmonary stenosis with intact ventricular septum, right heart catheterization was performed in conjuction with routine clinical and laboratory evaluation. Particular emphasis on the possible correlation of the systolic pressure recordings in the right ventricle and electrocardiographic manifestations will be presented.

Fatigue, exertional shortness of breath and the absence of cyanosis seem to be outstanding in the symptomatology. A systolic murmur was present in all with a thrill in one half of them, and an absent second pulmonary sound in 5. Poststenotic dilatation of the pulmonary artery was seen roentgenographically in 9 of the 10 patients.

If the systolic pressure in the right ventricle was at levels below 40-50 mm. Hg, only a double small R-R′ existed in the V-1 leads and little change from normal was observed. In the 50-75 mm. Hg range, the R waves were slightly more prominent in V-1 with the appearance of more prominent S waves in V-6. In the 75-100 mm. Hg range, the R waves in V-1 were increased in magnitude but were below 12 mm. With a systolic pressure between 100-150 mm. Hg, the R in V-1 tends to be 20 mm., or greater. With right ventricular pressures above 150 mm. Hg, the R waves were 20 mm. or more, and were accompanied by inversion of the T waves or S-T segment depression.

These electrocardiographic findings tend to correlate with the systolic pressures in the right ventricle and give a clue as to the ultimate severity of the lesion.

Study of the Use of Quinidine in Established Atrial Fibrillation and Atrial Flutter

Tsung O. Cheng, Baltimore, Md.

The purpose of this communication is to present the results of oral quinidine therapy in 121 patients with established atrial fibrillation and flutter, with special reference to interrelationship between serum concentration and dose and some interesting electrocardiographic observations.

The average serum concentration rose with increasing doses of quinidine till a "plateau" was reached, beyond which further increase in serum concentration could not be achieved despite the continuation of the same dosage schedule, although blood levels would rise if either the individual dose was increased or the same dose was given at a more frequent interval. If conversion did not occur with moderate serum concentrations, boosting up the dose and thereby raising the blood level seldom resulted in conversion but increased the incidence of toxicity.

During quinidine therapy of atrial fibrillation, an intermediary stage of atrial flutter was often observed. Contrary to what most cardiology textbooks stated, the appearance of atrial flutter in itself should not be a contraindication to further use of quinidine.

Prolongation of Q-T interval has long been accepted as being produced by quinidine administration. In this study it was found that the Q-T duration was normal in 85 per cent of the quinidine-treated patients. The typical electrocardiographic pattern produced by quinidine consists of depression of the S-T segment, lowering and inversion of the T wave, and increase in amplitude and premature take-off of the U wave, so that when the Q-U interval was taken to represent the Q-T interval proper, a "pseudo-prolongation" of Q-T interval resulted. It is advocated that an electrocardiogram be employed to guide quinidine therapy when facilities for determination of serum quinidine level are not available.

Preliminary Report of a Double Blind Evaluation of Ligation of the Internal Mammary Arteries

Leonard A. Cobb, George I. Thomas, Robert A. Bruce, and K. Alvin Merendino, Seattle, Wash.

Seventeen patients with incapacitating angina pectoris attributed to coronary atherosclerosis were invited to participate in an investigation of the efficacy of ligation of the internal mammary arteries for relief of symptoms. At the time of operation, the surgeon was presented with a card from a sealed envelope, chosen at random, instructing him whether or not to ligate the exposed arteries. The physicians re-evaluating the patients were not informed as to what was done at surgery.

From 2 to 9 months postoperatively, approximately two-thirds of the patients in each group reported significant subjective improvement ranging from 40 to 100 per cent. There was poor correlation between the patients' subjective improvement and the recorded use of nitroglycerin tablets in both groups. Postoperatively there was no apparent change in electrocardiograms recorded at rest and during exercise on the treadmill. Only 1 patient was able to walk on the treadmill for a significantly longer period after surgery. This patient experienced prompt symptomatic relief postoperatively and returned to full-time work; although his internal mammary arteries were not ligated, he has continued to be free from angina 7 months after surgery.

These preliminary observations do not support the claim that the relief of symptoms following

ligation of the internal mammary arteries is dependent upon increased myocardial blood flow. It is suggested that the subjective benefit is predominantly psychotherapeutic.

Simultaneous Estimation of Hepatic Blood Flow in Dogs by Means of I^{131} Labeled Rose Bengal (I^{131} RB) and Bromsulphalein (BSP)

Marton Combes,† Dallas, Texas

Fifty-six simultaneous estimations of hepatic blood flow (EHBF) utilizing I^{131} RB and BSP were obtained in 8 anesthetized dogs (Nembutal 30 mg. per Kg.) during hepatic vein catheterization. Intravenous "priming" doses of I^{131} RB (2 to 7 μc., equivalent to 0.02 to 0.40 mg. of Rose Bengal) and BSP (50 mg. per 10 Kg.) were followed by constant infusions (Bowman pump) of these substances: I^{131} RB 0.14 to 0.32 μc., equal to 0.003 to 0.04 mg. of Rose Bengal, per minute; BSP 0.3 to 0.7 mg./10 Kg. per minute), and after 20 to 30 minutes to allow for equilibration, femoral arterial and hepatic venous blood samples were obtained at intervals. The content of I^{131} RB (well scintillation counter) and BSP (colorimeter) in each blood sample was determined and separate values for EHBF were calculated from the hepatic clearance and extraction of each of these dyes.

The mean value of the ratio of:

$$\frac{EHBF\ \ BSP}{EHBF\ I^{131}\ RB}$$

was 0.99 ± S.D. 0.15 (range 0.70 – 1.35). No significant difference in:

$$\frac{EHBF\ \ BSP}{EHBF\ I^{131}\ RB}$$

from 1.0 was noted at arterial BSP concentrations of 0.4 to 1.0 mg. per cent (ratio 0.98 ± S.D. 0.15), and 1.0 to 1.8 mg. per cent (ratio 1.0 ± S.D. 0.32). Thirty-three of 56 of the individual comparisons (59 per cent) agreed within ± 10 per cent, 47 of 56 (84 per cent) within ± 20 per cent and 52 of 56 (93 per cent) within ± 30 per cent.

These data indicate that I^{131}-labeled Rose Bengal is a satisfactory substance for the estimation of hepatic blood flow in dogs. Because of the accuracy with which the I^{131} can be detected, they suggest that this compound will be of value in measurement of liver blood flow in the presence of lipemia, jaundice, and hemolysis, conditions that interfere with the accurate determination of *BSP*.

Selection of a Test for the Control of Oral Anticoagulant Therapy

W. Ford Connell and George A. Mayer, Kingston, Ontario, Canada

The Quick one-stage prothrombin test is still widely used for the control of oral anticoagulant therapy. It possesses certain obvious deficiencies:

1. In animal studies, intravascular thrombosis has been produced readily, after Dicumarol has been given in doses producing therapeutic prolongation of the prothrombin time.

2. In all large studies, both thromboembolic complications and hemorrhagic accidents occur when the prothrombin time has been maintained in the therapeutic range.

Five years ago, during studies with heparin, one of us (G.A.M.) developed the Standard Clotting Time. This test was found to be influenced significantly by therapeutic doses of various oral anticoagulants. We now report:

1. There is no significant correlation between the Standard Clotting Time (SCT) and the Quick one-stage test (PTR).

2. In 792 patients, on 6 different oral anticoagulants, significant prolongation of the SCT was demonstrated.

3. We observed no thromboembolism or hemorrhage when the SCT was within our therapeutic range.

4. With all anticoagulants used, we found a "lag period" of from 3 to 6 days before significant SCT prolongation was manifest. We have not yet found a "quick acting" oral anticoagulant!

After an 18 months' study of the 2 tests, performed concurrently, we proved that the SCT was the more reliable. In the past 3 years, 527 patients have been treated with various oral anticoagulants, the Standard Clotting Time being the sole therapeutic control. Clinical results have been excellent.

Chronic Idiopathic Pericardial Effusion

Daniel C. Connolly, Rochester, Minn., Thomas J. Dry, Rochester, Minn. and Cape Town, South Africa, Howard B. Burchell, C. Allen Good, and O. Theron Clagett, Rochester, Minn.

The diagnosis of chronic idiopathic pericardial effusion has been made in 6 patients since 1954. In none of the patients was there evidence of cardiac tamponade. All patients were women between 40 and 64 years of age at the time of diagnosis. The duration of pericardial effusion varied from 6 months to 8 years, as determined by serial x-ray films of the thorax. In each case, the diagnosis was suspected because of the x-ray finding of progressive enlargement of the cardiac shadow without symptoms or signs of cardiac failure.

Clinical examination and electrocardiograms did not provide information of diagnostic importance. In 5 of the 6 patients, angiocardiography was performed and was an important aid to diagnosis. None of the patients showed evidence of active tuberculous or rheumatic disease, and there was no

history of acute pericarditis. Exhaustive efforts to determine the etiology were unsuccessful. Hypothyroidism was excluded as a possibility, and the results of tests for lupus erythematosus were negative.

In 5 patients, surgical exploration of the pericardium was carried out with evacuation of the fluid and creation of a "window" between the pericardium and left pleural cavity. Neither examination of the pericardial fluid nor pericardial biopsy gave any indication of the etiologic factors. Evidence of constrictive pericarditis did not develop in any patient and pericardial effusion did not recur during the follow-up period.

Current Status of the Surgical Treatment Of Acquired Aortic Stenosis

John E. Connolly and David L. Bruns, San Francisco, Calif.

The surgical results in the correction of congenital aortic stenosis have in recent years been very encouraging. However, the patient with acquired aortic stenosis continues to be a dilemma to the cardiologist and cardiac surgeon.

In an effort to obtain a clearer picture of the natural history of acquired aortic stenosis we have reviewed the pathologic records of patients dying of proven aortic stenosis at Stanford University Hospitals. The incidence of concomitant mitral stenosis and its severity has been noted. During the past 2 years, direct percutaneous needle puncture of the left ventricle has been employed in the study of all candidates for aortic valvulotomy. Pre- and postoperative left heart catheterization results have been correlated with the anatomic findings at operation.

A plea will be made for early operation before severe calcification occurs and before decompensation is evident. The direct vision open approach has definite advantages over past blind technics, but only when used in the light of these criteria.

Activation of the Free Wall of the Right Ventricle in Experimental Right Bundle Branch Block

Loyal L. Conrad and T. Edward Cuddy, Oklahoma City, Okla.

In experimental right bundle branch block (RBBB), delay in activation of the right ventricle (RV) is produced largely by unidirectional activation of the ventricular septum. To determine if alterations in endocardial spread and ventricular conduction also exist, 10 experiments using quadripolar electrodes to record potentials from the RV of dogs were performed. Four electrodes were inserted in the apical and conus regions of the RV, 1 pair close to the septum and 1 pair in the free wall. The peak of R at each point from endocardium to epicardium was measured with respect to a reference electrode in the left ventricle before and after RBBB and after DC stimuli applied to each subendocardial point.

After RBBB accession spread radially from the earliest point activated and tangentially to later regions, endocardial activation preceding epicardial. In controls, spread was more nearly radial from endocardium to epicardium in all regions. The earliest endocardial point activated remained unchanged after RBBB (apical region near septum) but the latest point activated changed from apical free wall to conus.

Endocardial spread was slower after RBBB. Conduction through a specialized system was either absent or greatly altered. The pattern of activation following stimulation of an appropriate endocardial point resembled spread after RBBB.

An R was recorded from 159/160 electrode points throughout the RV wall. The pattern of intramural spread, particularly after RBBB, precluded estimation of RV thickness by measuring the time of onset of the intrinsic deflection. Bipolar leads did not contribute additional information.

Arterial Rigidity in Hypertension

James Conway, Ann Arbor, Mich., Eileen Busby, London, England, and Sibley W. Hoobler, Ann Arbor, Mich.

In view of the importance of arterial degenerative vascular diseases in hypertension, an attempt has been made to develop a clinical test by which it may be possible to detect changes in the elastic properties of the great vessels.

The test showing most promise depends upon changes in pulse pressure which occur as the diastolic pressure is suddenly reduced by inhalation of amyl nitrite. Since the publication of the details of the method, an unselected group of 70 hypertensive patients has been investigated. The results show that most patients with renal hypertension have normally elastic arteries, while those with essential hypertension usually have increased rigidity of the large arteries.

Patients with rigid arteries have, as would be expected, high systolic pressure and moderate elevation of diastolic pressure. The cardiac output, determined by the dye method, is in the normal range but the total peripheral resistance is increased (range 1370-2270 dynes/cm.$^{-5}$).

It is of interest to find that rigidity of the arterial tree is associated with other evidence of arterial degeneration—unfolding of the aorta, cerebrovascular and coronary disease. The incidence of these complications is twice as high in hypertensive

with rigid arteries as in those with normally elastic vessels. It has also been found that a positive family history of cardiovascular disease is more frequent in patients with rigid arteries and they have a greater fall in blood pressure in response to bed rest and to test doses of ganglion blocking agents.

Selective Left Ventriculography in the Assessment of Complex Congenital Cardiac Anomalies

Theodore Cooper and Andrew G. Morrow, Bethesda, Md.

Serial biplane radiography, following the selective injection of radiopaque dye into the left ventricle, permits visualization of normal and abnormal patterns of outflow from this chamber. This procedure was employed in 19 patients in whom an unusual ECG, equivocal indicator dilution study or catheterization data indicated the necessity of additional preoperative data. The patients ranged in age from 14 months to 42 years. In 16, the left ventricle was entered through an interatrial or interventricular septal defect during right heart catheterization. In 3 instances, the catheter was passed in a retrograde manner into the left ventricle from the aorta. Seventy per cent sodium acetrizoate, 1 ml. per Kg. but not exceeding a total dose of 60 ml., was injected rapidly, under a pressure of 10 Kg. per cm.^{2} Films were simultaneously exposed in the A-P and lateral projections. These studies permitted the identification of 7 incomplete (ostium primum) and 6 complete persistent atrioventricularis communis defects; there were 3 ventricular septal defects associated with atrial septal defect, 2 ventricular septal defects associated with transposition of the great vessels, and 1 instance of supravalvular aortic stenosis associated with a coarctation and aneurysm of the aorta. Injections were accompanied by a brief period of cardiac irregularity, followed by a rapid restoration of regular rhythm. Complications were limited to an intramural extravasation of dye associated with transient ventricular tachycardia lasting 6 seconds in 1 instance and the appearance of a transient supraventricular tachycardia in another patient. Left ventricular selective angiography has been found a valuable adjunct in the precise characterization of the complex anomalies involving abnormal left ventricular outflow.

Digitalis Requirements After Rapid Digitalization

Herbert W. Copelan, Philadelphia, Pa.

There is disagreement regarding the need for redigitalization with long-acting digitalis after initial rapid digitalization for cardiac decompensation. To resolve this problem, the authors studied 12 consecutive patients requiring digitalization for cardiac decompensation with stable sinus rhythm or established atrial fibrillation. Though limiting the number of patients acceptable for study, all of the following rigid criteria were met by each case. The patients had not recently received digitalis, had stable cardiac disease, and were free of other acute disease.

All patients were initially digitalized rapidly with intravenous deslanoside and simultaneously started on standard maintenance dosage of digitalis leaf. No other therapy was used. Physical activity was not reduced below the level performed before the start of treatment. Thus, any improvement observed could reasonably be attributed to digitalization.

The cases separated sharply into 2 groups. All 5 patients with sinus rhythm maintained their restored compensation on maintenance digitalis alone and did not require supplemental dosage. All 7 patients with atrial fibrillation required redigitalization, as indicated by rapid ventricular rates recurring a few days after initial rapid digitalization.

This study suggests that continuous full digitalization levels are necessary to control the ventricular rate in cardiac decompensation associated with atrial fibrillation. Presumably full digitalization levels are needed to suppress the atrioventricular node. With sinus rhythm, cardiac compensation, once restored, can be maintained by maintenance digitalis dosage alone, despite the assumed lack of continuous full digitalization levels. Possibly the inotropic effect of digitalis occurs at levels below full digitalization after compensation is restored.

Vasopressor Therapy of the Cardiac Arrhythmias

Eliot Corday, John H. Williams, Herbert Gold, and Joshua Fields, Los Angeles, Calif.

Supraventricular and ventricular arrhythmias may cause serious disturbances of the hemodynamics including hypotension, and when this occurs it results in coronary insufficiency, cerebral vascular insufficiency, renal insufficiency and liver necrosis. These observations have given new physiologic support for the pressor treatment of arrhythmias.

Vasopressor drugs may successfully terminate arrythmias or correct the severe hypotensive state until anti-arrhythmic agents have taken effect. We have shown that such supportive therapy will reduce the high mortality rate when tachycardia is associated with myocardial infarction. We have also been able to terminate premature ventricular systoles, auricular tachycardia, flutter and fibrillation, and ventricular tachycardia and correct sinus bradycardia in some patients and experimental ani-

mals without the use of antiarrhythmic drugs by elevating the systemic blood pressure with pressor agents. These arrhythmias could also be abruptly corrected in the hypotensive dog by restoring the blood pressure by application of an aortic snare, after the vagus nerve was cut or after the heart was completely denervated. This would suggest that the pressor effect acts, in some unknown fashion, directly upon the heart to abolish the arrhythmia.

However, the vasopressor drugs which may abolish arrhythmias may also cause serious arrhythmias if the blood pressure is raised too high. We reviewed 242 experiments in which vasopressor drugs were utilized and noted that these arrhythmias may occur when the blood pressure has been elevated above 180 mm. Hg. Therefore, whenever pressor drugs are administered, their effect should be carefully monitored to prevent severe hypertension and the development of serious arrhythmias.

Abnormal Behavior of Pulmonary and Brachial Artery Pressures during the Valsalva Maneuver in Patients with Emphysema

Richard S. Cosby, Lawrence Herman, Louis Freibrun, and Mary Mayo, Los Angeles, Calif.

The characteristic response of the peripheral artery pressure to forced straining in patients with emphysema was studied by measuring simultaneously pulmonary and brachial artery pressure curves in patients with (1) emphysema, (2) mitral stenosis with pulmonary hypertension, and (3) left ventricular failure. The normal response of the pulmonary artery to the Valsalva maneuver consists of (1) a very slight initial rise of pressure during strain; (2) a marked fall with a marked decrease of pulse pressure; and (3) a rise of peripheral pressure and widening of the pulse pressure after strain, with bradycardia. During strain the right atrial pressure rises markedly so that after strain the rise of right ventricular pulse pressure is most likely due to a rapid increase in stroke volume.

In a group of 30 patients, 6 presented the characteristic "emphysema response." The pulmonary artery pulse pressure narrows markedly during the strain period, while the mean pressure remains elevated. After strain, the pulse pressure remains narrow and tachycardia rather than bradycardia is present. The pulse pressure only returns to normal as the systemic artery pressure rises. Furthermore, in patients with severe emphysema, a striking step-like ascent of both systemic and pulmonary artery pressures occurs at each respiration during the recovery period. The abnormal physiologic events described, particularly the marked simultaneous decrease of pulmonary and systemic pressure at the end of the period of strain, are consistent with markedly diminished right heart filling and may be closely related to the diminished lung elasticity in emphysema.

Early Diastolic Third Heart Sounds in the Right Supraclavicular Fossa

Anthony M. Cosentino, San Francisco, Calif., David Y. Naruse, San Mateo, Calif., and Elih York, San Francisco, Calif.

The authors have described the occurrence of early diastolic third heart sounds in the right supraclavicular fossa when inaudible at the apex. The patients in whom this phenomenon was noted were all in both right- and left-sided congestive heart failure. Phonocardiograms gave graphic confirmation of this finding in 3 instances. However, it was detected by the stethoscope in 7 instances. The discrepancy is probably due to the anatomic difficulties encountered in the right supraclavicular fossa by the phonocardiographer. No actual attempt was made to evaluate the frequency of this finding. However, the cases were collected over a 3-month period, January to April 1958, from the patients admitted to the Medical Service of the San Francisco Veterans Administration Hospital.

Recently, one paper has emphasized the occurrence of presystolic third heart sounds in the right supraclavicular fossa. However, mention of an early diastolic, or so-called protodiastolic third heart sound being heard anywhere but at the apex could be found by the authors in only one obscure publication.

The authors feel this physical finding is of aid to the clinician in the evaluation of cardiac patients and have pursued this study in an attempt to popularize this phenomenon.

Surgical Treatment of Occlusive Lesions Occurring in Major Branches of Aortic Arch and Internal Carotid Arteries

E. Stanley Crawford, Michael E. De Bakey, Denton A. Cooley, and George C. Morris, Jr., Houston, Texas

Recent arteriographic studies have shown that occlusive lesions causing cerebral arterial insufficiency are located in the extracranial portion of these vessels in a relatively high proportion of patients with this condition. In most of these cases the lesion is discrete and localized to the origin of the internal carotid artery. In some instances, however, the occlusion may be located at the origin of the major vessels arising from the aortic arch. The manifestations of arterial insufficiency vary in these cases according to the location of the lesion. Occlusions of the internal carotid artery are asso-

ci ed with visual and neurologic disturbances. L ions located at the origins of the great vessels a ing from the aortic arch may be associated with si ilar disturbances as well as arterial insufficiency o the upper extremities. The diagnosis and pre- ci location of these occlusive lesions may be read- il established by angiographic studies.

The location and discrete nature of these lesions p mit direct surgical attack and restoration of n mal circulation by either thrombo-endarterec- t ay or bypass graft. This report is concerned w h an analysis of the problem and the successful a plication of these technics in the treatment of 5 cases. Arterial insufficiency of both the cere- b m and upper extremities has been relieved in th majority of these cases, demonstrating the e fectiveness of this approach to an otherwise dis- m l problem.

Atypical Patent Ductus: Use of a Vasopressor Agent in Diagnosis

Lamar E. Crevasse, Gainesville, Fla., and R. Bruce Logue, Emory University, Ga.

Five per cent of patients with patent ductus have atypical murmurs. There may be no murmur, a pulmonic systolic flow murmur or a late systolic-early diastolic murmur overriding the second sound. When atypical murmurs are present, several situations exist: (1) the ductus may be extremely small or quite large; (2) in infants with low systemic blood pressures and relatively high pressures in the pulmonary artery, the magnitude of the systolic-diastolic pressure gradient may be quite small, producing turbulence of blood flow in late systole or not at all; (3) when pulmonary hypertension complicates patent ductus, the magnitude of the pressure gradient may be sharply reduced or obliterated; (4) patent ductus, when complicated by an additional cardiovascular lesion, most commonly coarctation of the aorta, is usually atypical.

It is apparent that the size of the ductus and the pressure relationships between the aorta and pulmonary artery will dictate the type of murmur present. Following the suggestion of Bing, we have employed a vasopressor agent (mephentermine) to raise rapidly aortic pressure and thereby create or widen the systolic-diastolic pressure gradient across the ductus. This produces the continuous machinery murmur in atypical cases. It is a valuable aid in diagnosis without the expense of catheterization, and we have employed this method in 12 atypical cases confirmed by operation.

Phonocardiograms of the graphic features before and after alterations of aortic pressure will be used to demonstrate the auscultatory changes of atypical cases.

Pulmonic Stenosis: Auscultatory and Phonocardiographic Characteristics

Lamar E. Crevasse, Gainesville, Fla., and R. Bruce Logue, Emory University, Ga.

From an auscultatory and phonocardiographic point of view, pulmonic stenosis with intact ventricular septum may be classified as mild, or moderate to severe. In mild stenosis the first heart sound is followed by an early systolic ejection sound which disappears with inspiration and returns with expiration. Simultaneous pulmonary artery and phonocardiographic tracings have revealed this sound to occur .06 to .08 second after rise of pulmonary artery pressure; there is a striking correlation with the respiratory cycle suggesting it is related to mechanical respiratory tension alterations of the poststenotic pulmonary artery, as it is present over the naked pulmonary artery at operation. The pulmonic second sound is pathologically split, ranging from .04 to .08 second from the aortic component. This is related to pulmonic obstruction and delay in right ventricular ejection and subsequent closure of the pulmonic valve. Right ventricular systolic pressure is usually less than 80 mm. Hg.

In moderate to severe pulmonic stenosis, the bulk of the systolic murmur is delayed overriding the aortic component of the second sound and closure of the pulmonic second sound is delayed .10 to .14 second after the aortic component. Right ventricular pressure is usually greater than 100 mm. Hg. We have been able to corroborate Leatham's observations that there is a close linear relationship between the delay of right ventricular ejection (aortic-pulmonic interval) and right ventricular systolic pressure. This is a rapid method for determining right ventricular systolic pressure without catheterization and is more reliable than the height of the R wave in V_1. When a ventricular filling sound (S_3) is present with moderate to severe pulmonic stenosis, an atrial septal defect is usually associated with it. The auscultatory and graphic features, mechanism of the pulmonic ejection sound and correlations of right ventricular systolic pressure with the aortic-pulmonic interval will be demonstrated by catheter and phonocardiographic material.

Treatment of Severe Aortic Regurgitation by Hufnagel Valve with Subsequent Term Pregnancy

James E. Crockett, C. Frederick Kittle, and E. Grey Dimond, Kansas City, Kans.

This report summarizes the experience with a 19-year-old female who suffered from aortic regurgitation with angina pectoris and congestive heart failure manifested by repeated episodes of

pulmonary edema, cardiomegaly, hepatomegaly and pedal edema. Angina pectoris was frequent and severe. Blood pressure was 130/0 with classic clinical findings of aortic regurgitation. Cardiac fluoroscopy and electrocardiogram revealed marked left ventricular hypertrophy. Following compensation, a Hufnagel valve was inserted into the aorta. The patient remained compensated following surgery and became pregnant several months later. Under careful management, this pregnancy was completed without evidence of congestive failure or angina and delivered by caesarean section. Patients with aortic regurgitation, angina and congestive heart failure have a uniformly poor prognosis without the additional circulatory burdens imposed by pregnancy. Improvement in the functional status of such patients following the insertion of a Hufnagel valve has been observed frequently, but this is the first patient known to carry a pregnancy successfully to term following this procedure. This is a striking demonstration of the efficiency of this valve in correcting the abnormal cardiovascular state in severe aortic rgurgitation.

Alteration of Electrocardiographic Pattern and Cardiac Rhythm by Adrenal Steroids in Normal and Adrenalectomized Dogs

Henry C. Crossfield, John P. DaVanzo, and Wilbur W. Swingle, Princeton, N. J.

Toxic doses of 2-methyl-9α-fluorohydrocortisone (2-methyl FF), administered to normal dogs, induced lowering and broadening of the T waves. Toxic doses of desoxycorticosterone (DOC), produced inverted T waves. When given in large doses, l-dehydrohydrocortisone (prednisolone) caused the T waves to become sharply pointed and often diphasic with S-T depression.

Adrenalectomized dogs in insufficiency first developed T and S-T changes followed by disappearance of the P waves and finally ventricular rhythm appeared. Occasionally a small R and large S developed instead of the more usual T and S-T changes.

Dogs lacking adrenals but maintained on DCA therapy when subjected to the stress of 20 minutes of intestinal stripping, developed severe shock with drastic decline in blood pressure. Though the ECG pattern revealed insignificant changes there were periods of asystole which disappeared following injection of glucocorticoids. Corticoids vary greatly in their ability to restore the ECG to normal. Mineralcorticoids had little effect in fasted animals so treated whereas the glucocorticoids such as 2-methyl FF, were very effective both in restoring activity and vigor of the fasted dog and returning the ECG to normal. A combination of glucocorticoid and aldosterone proved most effective.

There was partial correlation of various blood tests including blood urea N., electrolytes and plasma volume, with changes in different portions of the electrocardiograph.

Constant Volume Fractional Sample Collector for Repetitive Cardiac Output Determinations

David W. Cugell, M. Mostafa Abdel-Fattah, and Margaret E. Gantt, Chicago, Ill.

Continuous recording methods have greatly simplified cardiac output determinations but require much larger doses of radioactive substances or of special dyes than multiple sample technics. These large dose requirements limit the number of times the cardiac output determination can be repeated. A greater number of cardiac outputs can be performed with safety if multiple samples are collected, but the handling and manipulation of each sample is burdensome.

An apparatus has been devised which will collect as many as 60 consecutive, discrete arterial blood samples of constant volume, at any rate up to 0.5 second per sample. Either test tubes or planchets suitable for automatic scintillation counting may be used. The sample size may be as large as 0.7 ml. The radioactivity of samples collected from a reservoir were not significantly different ($p > 0.3$) at delivery pressures of 200 mm. Hg (496 counts per minute S.E. = 5) and 50 mm. Hg (489 counts per minute S.E. = 6). Flow determinations were made with the fractional sample collector from a mechanical analogue of the circulatory system which provided re-circulation of the injected tracer. Flow rates were varied from 1.5 to 3.7 L. per minute. There was close agreement between the calculated and the measured flow rates (mean differences = 0.05, S.E. = 0.03). Satisfactory cardiac outputs can be determined on patients with 2-4 μc. of radio-iodinated serum albumen if the samples are measured in a well counter (70 per cent efficiency). The samples are placed directly into the counting equipment. Whole blood rather than plasma may be used and no preliminary volume adjustment is necessary.

Pulseless Disease: Observations on Eleven Patients with Three Autopsies

James H. Currens, Boston, Mass., and William M. Thurlbeck, Boston, Mass. and London, England

Pulseless disease (aortic arch syndrome) results from occlusion of the great vessels at their origin from the aortic arch. Robert Adams described one case in 1827. Eleven patients have been observed in whom diminished or absent arterial pulsations have been apparent in 1 or both arms. Carotid pulsations were absent in 5 patients.

The ages ranged from 46 to 81 and the sex distribution was about equal. The following conditions were noted in these 10 patients: coronary heart disease (9), claudication (5), stroke (3), Cheyne-Stokes breathing (3), intermittent blindness (3), diabetes (1), syphilis (1) and cataract ( ).

The blood pressure was determined satisfactorily by a machine devised to record the Karatkov vibrations over the brachial artery. The blood pressure was low or normal in 10 patients and elevated in 1.

Three autopsied cases have demonstrated evidence of severe atherosclerosis with associated thrombosis of the great vessels at the aortic arch without evidence of arteritis. The retinal vessels of 1 patient had innumerable minute aneurysms demonstrated at autopsy.

Severe aortic atherosclerosis and thrombosis were the common cause of pulseless disease in these investigations. Long-term anticoagulation with Dicumarol in 3 patients has resulted in some clinical improvement.

Experimental Delayed Occlusion of the Left Coronary Artery

George R. Daicoff, Norman Siderius, Chicago, Ill., Peter L. Brunnen, Aberdeen, Scotland, Roger D. Pine, and Peter V. Moulder, Chicago, Ill.

Reconstitution of the blood supply to the heart in coronary heart disease by direct means, i.e., endarterectomy, replacement grafting and bypass grafting, has become technically feasible. The general acceptance of these procedures has been hampered by the problem of reliable experimental evaluation. A method of slowly occluding the main stem left coronary artery in the closed-chest, awake dog has been developed to assess the benefits of such procedures. Occlusion of the main stem left coronary artery, which in the dog is extremely short (1-4 mm.), leaves proximal vessel of adequate size for the direct surgical approach.

A ligature was passed around the left coronary artery and a wafer of Ameroid, a hydrophilic, slowly expanding, casein plastic, was tied down over the vessel. As the wafer expanded, the ligature tightened and occluded the vessel.

Twenty of 29 dogs prepared in this manner developed severe occlusion of the left coronary artery and died between 4 hours and 10 days. The other 9 animals demonstrated minimal occlusion of the coronary artery and survived. Serial ECG's showed transient S-T changes in all, and ventricular arrhythmias in those with severe occlusion. No ECG infarction patterns were produced. Ventricular fibrillation was demonstrated in 4 dogs. The surviving 9 dogs in this series showed minimal occlusion. Myocardial infarction was not found in any of the hearts by gross inspection or on microscopic study.

Effects of Estrogen Therapy on the Ballistocardiogram in Patients with Coronary Heart Disease

Frank W. Davis, Baltimore, Md.

As part of a many-faceted long-range study of patients with coronary heart disease, a small number of individuals have been given estrogenic agents. The effects of this therapeutic program have been monitored by over-all clinical response, electrocardiograms, ballistocardiograms, ballistocardiographic cigarette tests, and a battery of serum lipid studies. This presentation will summarize the effects on the ballistocardiogram of conventional estrogens and of synthetic agents designed to preserve serum lipid evidence of estrogenicity while attempting to minimize clinical feminization.

A total of 44 patients have received these agents for an average of 15 months, with a range of 3 to 51 months. The influence of therapy on ballistocardiographic form was classified as improved, unchanged, or worse. For comparison, 5 per cent of untreated patients, followed in the same manner, were known to show spontaneous BCG improvement over a 2-year period. Seventy-three per cent of patients who received feminizing doses of ordinary estrogens demonstrated improvement in BCG form over an average treatment period of 20 months. Fifty-eight per cent of subjects given an experimental compound of estrogenic nature showed improved patterns during an average of 13 months of therapy.

In the former group (ordinary estrogens) serum lipid pattern became normal in all instances. In the latter, patients lipid pattern improved in the majority, but serum lipid response did not necessarily correlate with BCG alteration. Clinical improvement, in general, was observed in patients whose ballistocardiograms improved.

The mechanism of estrogenic effect on the BCG is not known, but it is felt that a basic alteration in cardiodynamics is suggested by this change. Whether this is elicited by structural alteration in coronary atheromata, changes in blood viscosity, or some unknown factor, remains to be determined.

Characteristics of Heart Sounds by Intracardiac Phonocardiography

George W. Deitz, David H. Lewis,† Philadelphia, Pa., John D. Wallace, and James R. Brown, Jr., Johnsville, Pa.

Since the introduction of intracardiac phonocardiography by ourselves in 1956, sounds and mur-

murs can be more accurately localized. The intensity of all sounds is greater in the left side than the right. Low frequency components are heard and recorded throughout the heart sounds. The higher frequency components of the first sound are 4 in number. Simultaneous recordings from both the left and right ventricles reveal these components to be mitral closure, tricuspid closure, pulmonic opening, and aortic opening in that order. The second sound is composed of 2 major vibrations, first aortic valve closure and then pulmonic valve closure. Inspiratory separation of these sounds occurs normally. Transient incomplete right bundle branch block produced during catheterization did not alter the splitting of the second sound nor did it alter the onset of the first sound in the right ventricle.

Ejection clicks occur after semilunar valve opening and coincide with the rapid ejection period into the great vessels. The opening snap of mitral stenosis was not recorded in the left ventricle despite the fact that it was seen in simultaneous chest recordings. It is possible that this sound originates in the left atrium and is reflected back into that chamber and not forward into the ventricle. In like manner, a left ventricular gallop was not transmitted forward into the ascending aorta despite the fact that it was well recorded in simultaneous chest tracings.

Intracardiac phonocardiography has increased our knowledge of the nature of normal and abnormal heart sounds.

Phonocardiogram in Pure Mitral Regurgitation

Madhukar Deshmukh, Joseph F. Uricchio, and William Likoff, Philadelphia, Pa.

The occurrence of a midlate diastolic murmur and opening snap with a loud systolic murmur at the apex of the heart in the past has always been associated with the presence of organic mitral stenosis in association with mitral regurgitation. Ten cases, however, are reported in which the opening snap and mid-diastolic murmur were present in pure mitral regurgitation without any demonstrable mitral stenosis. In these cases, the first heart sound was delayed beyond the normal range of 0.06 second after the inscription of the QR complex. The diagnosis of pure mitral regurgitation was confirmed in all these at surgery and on postmortem examination in one.

The hemodynamic studies in pure mitral regurgitation are presented which reveal an increase in mean left atrial pressure and a significant filling gradient across the mitral valve in early and middiastole. This gradient falls in late diastole, but in many instances does not fall to zero. This phenomenon offers the explanation for the delay in first heart sound as the left ventricle has to overcome this small gradient and exceed left atrial pressure to bring about closure of the mitral valve. In addition, valve mobility may be impaired because of leaflet thickening and calcification.

Current Aspects of Perfusion Equipment and Perfusion Physiology as Related to Open Heart Surgery

Richard A. DeWall, Herbert E. Warden, Richard L. Varco, and C. Walton Lillehei, Minneapolis, Minn.*

Extracorporeal attempts to duplicate the respiratory and cardiac functions is associated with many compromises from the actions of the normal intact heart and lung. Our recently acquired knowledge has allowed us to minimize these compromises and develop technics which provide access to the interior of the heart for reparative operations under direct vision. Many types of heart-lung machines have now been developed to serve as an aid to open heart surgery; however the success of each type would seem to be more dependent upon the talents of the people using any single apparatus rather than the inherent qualities of that system. We have a continuous program directed towards the improvement of methods for pumping and the oxygenation of blood as applied to ways in which such information may aid the cardiac patient. Parallel to our study of improved methods for extracorporeal circulation, considerable effort is directed towards the understanding of cardiac physiology in health, under surgical situations, and in failure.

The above described activities have been applied on over 500 patients undergoing reparative open intracardiac surgery. The helix reservoir bubble oxygenator was used in over 400 of these operations to support their respiratory function during the procedure. Much information has been gained from these perfusions which have aided in subsequent perfusions.

Evaluation of Internal Mammary Artery Ligation and Sham Procedure in Angina Pectoris

E. Grey Dimond, C. Frederick Kittle, and James E. Crockett, Kansas City, Kans.

Eighteen patients were selected for a "blind" study. All suffered from easily provoked angina a marked change in the electrocardiogram on exercise occurred in the majority. A skin incision was made in all 18; the actual ligation procedure was carried out in 13. The clinical cardiologist and

the patient did not know the selection. All have been followed from 6 to 18 months.

... marked improvement in the degree of angina occurred in 10 of the 13 actually ligated. Five patients had a sham procedure and all emphatically described marked improvement. Before and after surgery, all patients were exercised to the point of angina. In the majority, the same marked abnormality of change in effort EKG could be produced on the same degree of exercise although the increased resistance to angina was remarkable, ligated or sham. The need for nitroglycerin decreased; exercise tolerance increased significantly in 15 of the 18 patients studied; 10 of these were ligated, 5 were sham.

It is concluded that if the internal mammary artery procedure has any merit whatsoever, attempts to evaluate it in terms of increased exercise tolerance or decreased need for nitroglycerin ignore the psychogenic component of angina.

Coronary Visualization by Occlusion Aortography During Induced Cardiac Arrest in the Intact Subject

Charles T. Dotter and Louis H. Frische, Portland, Ore.

Attempts to visualize man's coronary arteries by thoracic aortography have been literally and figuratively washed out by aortic blood flow. Even alarmingly large doses of concentrated contrast media, used in a brute force effort to compensate for dilution, are largely swept out of the aorta to cause undesired systemic effects rather than coronary visualization.

These effects of blood flow are eliminated by injecting the contrast agent during a brief period of induced cardiac arrest in combination with total occlusion of the ascending aorta. Over 1,000 experimental studies in dogs and recent application to man reveal the approach to be safe, simple, reliable and highly effective.

The technic of examination is as follows: A double-lumen balloon catheter, introduced through a suitable peripheral artery, is maneuvered under fluoroscopy until its tip lies about an inch above the level of the aortic valves. A small dose of acetylcholine is injected through the catheter, almost instantly producing cardiac arrest, whereupon the balloon is rapidly inflated, contrast agent injected and serial films made. The arrest is self limited, reverting to normal sinus rhythm within about 8 to 15 seconds. Risk of the procedure is judged to be minimal while improvement in radiographic detail is striking. Intercoronary anastomoses are routinely demonstrated in normal dogs, as are major and minor abnormalities in the coronary arteries of man.

Occlusive Mean Gradient: Estimate of Diastolic Run-off from the Aorta

Paul Dreizen and R. J. Pearson, Jr., Bethesda, Md.

Inflation of a sphygmomanometric cuff about the arm to pressures between systolic and diastolic pressure resulted in elevation of mean pressure, recorded through an indwelling needle, in the brachial artery distal to the cuff. The maximal increment in mean pressure was termed the occlusive mean gradient (OMG).

The OMG was determined in subjects at rest, during exercise, and after the administration of nitroglycerin sublingually, methoxamine intramuscularly, and isoproterenol sublingually. In 37 control subjects (413 determinations), partial correlation coefficients indicated a significant relationship of the OMG to pulse pressure ($r = .57$), but not to diastolic pressure or age. In 20 subjects with aortic insufficiency or patent ductus arteriosus (193 determinations), the OMG was related to diastolic pressure ($r = -.34$), age ($r = .39$), as well as to pulse pressure ($r = .76$).

Although the OMG, at any pulse pressure, tended to be higher among subjects with aortic insufficiency or patent ductus arteriosus than among the control subjects, clear-cut differentiation of the 2 groups was achieved only after sublingual administration of nitroglycerin. Among 32 control subjects, the postnitroglycerin OMG did not exceed 14 mm. Hg, and averaged 9.5 ± 2.9 mm. Hg. Among 15 subjects with aortic insufficiency, the postnitroglycerin OMG varied from 15 to 53 mm. Hg, and averaged 25.2 ± 12.7 mm. Hg. Its magnitude related closely with the severity of aortic regurgitation as determined by clinical evaluation. In 2 subjects with patent ductus arteriosus, the postnitroglycerin OMG fell from 30 and 14 mm. Hg to 10 mm. Hg after surgical repair.

The postnitroglycerin OMG is suggested as a physiologic estimate of the presence and the extent of diastolic run-off of pressure from the aorta, occurring with aortic insufficiency, patent ductus arteriosus, and perhaps systemic A-V fistulae.

Conversion of Radioactive Dihydroxyphenylserine to Arterenol

William Drell,† Los Angeles, Calif.

Results from many laboratories indicate that 3,4-dihydroxyphenylalanine (DOPA) is probably the natural precursor of arterenol and epinephrine although 3,4-dihydroxyphenylserine (DOPS) can be decarboxylated directly to arterenol both in vitro and in vivo. When uniformly labeled, tyrosine is incubated with bovine adrenal slices in the presence of a DOPA decarboxylase inhibitor, radi-

oactive DOPA but not DOPS is accumulated. To confirm this specificity α-C^{14}-dl-*threo*- and dl-*erythro*-DOPS of high specific activity have been synthesized by modifications of Bolhofer's procedure. The *erythro* isomer was purified by chromatography on cellulose and alumina columns. The 2 compounds have been compared in rats and bovine adrenal slices and homogenates. The yield of labeled urinary arterenol from *threo*-DOPS administered i.p. to rats is slightly greater than that from *erythro*-DOPS and is decreased by the monoamine oxidase inhibitor, 1-isonicotinyl-2-isopropylhydrazine, whereas the amount formed from the *erythro* is unaffected by the drug. In further contrast, the activity of the arterenol derived from *erythro*-DOPS in vitro is considerably higher than that formed from the *threo-DOPS*, agreeing with earlier studies with unlabeled materials.

Differentiation of Interatrial Communications by Clinical Methods: Ostium Secundum, Ostium Primium, Common Atrium and Total Anomalous Pulmcnary Venous Connection

James W. DuShane, William H. Weidman, and John W. Kirklin, Rochester, Minn.

These various types of interatrial communications are associated with symptoms, signs, radiologic and electrocardiographic features which will permit correct differential diagnosis in most instances.

The fundamental hemodynamic alteration common to these anomalies is increased flow of blood through the right atrium, right ventricle and pulmonary circuit. A cleft in the aortic leaflet of the mitral valve occurs in association with ostium-primum defects and common atrium, but not with ostium-secundum defects and total anomalous pulmonary venous connection. A common mixing chamber for pulmonary and systemic venous blood exists in common atrium and anomalous pulmonary venous connection, with resultant systemic arterial oxygen unsaturation.

Symptoms are similar in patients with ostium-primum and ostium-secundum defects, consisting of mild fatigue with exercise, in most instances. Patients with common atrium usually have mild-to-moderate exercise intolerance, while those with anomalous pulmonary venous connection may be severely handicapped and fail to survive infancy, although those who do reach childhood may have only moderate disability.

Cardiac enlargement and a systolic murmur in the pulmonary area occur in all cases, whereas patients with ostium-primum defects and common atrium have an additional apical systolic murmur of mitral insufficiency. Radiologic evidence of increased pulmonary blood flow is a factor common to all. The electrocardiogram provides important information of diagnostic value, permitting separation of ostium primum and common atrium from the other 2 anomalies by employment of vectorial analysis of the QRS complexes in the frontal plane.

Significance of Renal Function Tests in Renal Hypertension

Harriet P. Dustan, Eugene F. Poutasse, Arthur C. Corcoran, and Irvine H. Page, Cleveland, Ohio

Occlusive lesions of renal arteries can cause remediable hypertension. This report compares function tests of individual kidneys in patients with essential hypertension and hypertension associated with pyelonephritis or angiographically demonstrated occlusive renal arterial lesions and evaluates the prognostic significance of these tests.

Urine flow (V), glomerular filtration rate (GFR), urine osmolality (U_{Osm}), urine sodium concentration (U_{Na}), and excreted fraction of the filtered sodium load (EF_{Na}) were measured during mannitol diuresis and pitressin antidiuresis.

The functions were equal bilaterally in 10 patients with essential hypertension. In 6 with pyelonephritis, GFR and V were depressed on the more affected side; other functions were nearly equal. A like pattern was demonstrated in 5 patients with occlusive lesions of a branch artery. In 6 of 7 patients with occlusive disease of one main renal artery, GFR, V, U_{Na} and EF_{Na} were depressed and U_{Osm} was increased on the affected side. This pattern suggests an over-all decrease in effective renal arterial pressure. In 7 patients with bilateral lesions, V paralleled changes of GFR, but changes in other functions were variable.

Remissions of diastolic hypertension have followed operations in 4 of 5 patients with unilateral lesions and in 3 of 5 with branch lesions. The functional patterns in these 2 situations are quite diverse as they are also in the presence of bilateral lesions. Hence, function tests supplement angiography but cannot, of themselves, indicate the nature of an arterial lesion or the likelihood of relief of hypertension by an appropriate surgical procedure.

Effects of Isoproterenol on Peripheral Venous Tone and Transmural Central Venous Pressure in Man

John W. Eckstein and William K. Hamilton, Iowa City, Iowa

The object of these studies was to determine whether peripheral venous dilatation or hyperventilation caused the fall in atrial pressure during isoproterenol infusion.

Venous pressure-volume curves were obtained plethysmographically from the right arm and

nous pressure was measured in the left arm fore and during isoproterenol chloride infusion 5.8 μg. per minute) into a foot vein. Active vasoconstriction occurred in each ($p < 0.001$) and nous pressure fell in 4 (unchanged in 1) of 5 periments ($p < 0.05$). Forearm venous blood lume averaged 3.8 ml. per 100 ml. of tissue during control periods and 2.2 ml. during infusions $p < 0.001$). Despite the fall in venous pressure, lood shifted from the extremities primarily because of venous constriction.

Right atrial pressure (Gauer's method) and trapleural (esophageal) pressure, and the resultant (transmural central venous pressure) were registered simultaneously with end-expiratory CO_2 concentration and ventilation before and during oproterenol infusion in 5 other experiments. Ventilation increased (average increase, 8.0 L. per minute) and end-expiratory CO_2 tension decreased (average decrease, 5.8 mm. Hg) in each test. Despite this hyperventilation, esophageal pressure remained practically unchanged. Atrial pressure fell regularly (average fall, 1.9 mm. Hg, $p < 0.02$), as did transmural central venous pressure (average fall, 1.9 mm. Hg, $p < 0.05$).

The central venous pressure fall with isoproterenol is not a respiratory effect nor the result of blood pooling in the extremities. Peripheral vasoconstriction may maintain the venous return and prevent an even greater pressure drop.

Postamputation Radiographic Evidence for Small Artery Obstruction in Arteriosclerosis

Edward A. Edwards, Boston, Mass.

Thirteen arteriosclerotic limbs were studied by radiography after injection of the mercury-barium emulsion of Reiner, Rodriguez and Jimenez. Six other extremities with presumably normal arteries were similarly examined to establish the normal pattern of the fine arteries. The injection filled the very small arteries and some arterioles.

Obstruction of the small named and unnamed arteries to the heel and toes were clearly shown. The pattern of occlusion was identical in the diabetic and nondiabetic limbs. The severity or diffuseness of occlusion was roughly the same except in a few nondiabetic limbs.

In 2 of the 13 cases, arteriovenous shunting was revealed at multiple sites in the tarsal area.

Hemodynamics in Labile Hypertension

Robert H. Eich, Richard J. Peters, and Richard I. Lyons, Syracuse, N. Y.

Although the hemodynamics in labile hypertension have been studied before, reliable methods for measuring cardiac output were not used and the results were somewhat inconclusive. It was felt to be of value, therefore, to restudy the problem using the dye-dilution technic to measure cardiac output. Twenty-five labile hypertensives selected at random were studied, 23 male and 2 female. For purposes of this study, labile hypertension was defined as an elevated blood pressure on the day of admission and at least one normal blood pressure during the next 3 days.

Thirteen of the subjects had a cardiac index over 4.5 L. per minute per $M.^2$ mean cardiac index 5.56 L. per minute per $M.^2$ and mean resistance 870 dynes $cm.^{-5}$ second. These values are significantly different from the normal ($p < .01$). In the remaining 12, the hemodynamics were those of essential hypertension, with a normal cardiac index (mean 3.56 L. per minute per $M.^2$) and elevated resistance (mean 1,371 dynes $cm.^{-5}$ second). In 4 subjects restudied during their hospitalization, the hemodynamics were the same.

Although for any 1 patient it was not always possible to predict the hemodynamics, the 2 groups were different clinically. Those with the high cardiac output were younger and had more evidence of vasomotor lability. Those with the normal output and high resistance had a stronger family history and higher incidence of complications.

The results suggest that the hemodynamics may differ in labile hypertension and their measurement may be of aid in prognosis and therapy.

Production of Heart Sounds by the Cardiac Catheter

Frederic L. Eldridge and Herbert N. Hultgren, San Francisco, Calif.

Increased interest in the correlation of heart sounds with mechanical events in the cardiac cycle has led to the simultaneous recording of intracardiac pressures and phonocardiograms in many laboratories. It has been observed in this laboratory that heart sounds may be produced by movement of a cardiac catheter within the heart, and that such sounds may lead to errors in the interpretation of phonocardiograms obtained during cardiac catheterization.

It was the purpose of this study to examine the incidence, characteristics, and mechanism of production of such catheter-induced heart sounds. Phonocardiograms were recorded in 55 patients during routine diagnostic cardiac catheterization studies. In 19 patients, loud early diastolic sounds were recorded from the left sternal margin. A characteristic pressure tracing occurred whenever the sound was produced. These tracings indicated that the catheter tip was in the pulmonary artery during systole. Abrupt withdrawal of the catheter tip from the pulmonary artery occurred in early or mid-diastole coinciding with occurrence of the sound. Systolic ejection advanced the catheter

tip into the pulmonary artery again. In 1 patient with valvular pulmonary stenosis, a mid-systolic sound occurred while the catheter tip remained in the pulmonary artery. In an excised canine heart with an intact, fluid-filled pulmonary artery, catheter passage across the pulmonary valve produced similar sounds.

It is concluded that movement of an intracardiac catheter through heart valves may produce true valvular heart sounds. These sounds may be identified by their timing and their association with a characteristic pressure tracing.

Electrocardiographic Evaluation of Pulmonic Stenosis

Mary Allen Engle, Tomiko Ito, Daniel S. Lukas, and Henry P. Goldberg, New York, N. Y.

Patients with pulmonic stenosis and intact ventricular septum often have similar symptoms and physical and roentgenographic manifestations despite differences in severity of stenosis. This poses a problem in selection of those needing cardiac catheterization in anticipation of surgery and in evaluation of postoperative results. It was decided to test whether electrocardiography fulfilled the need for a simple tool to reflect reliably the right ventricular burden.

Analysis was made of electrocardiograms taken close to the time of pressure recording (57 patients) or autopsy (9). Right ventricular systolic pressures ranged to 240 mm. Hg. Nineteen had mild stenosis (pressure below 80 mm. Hg), 14 had moderate stenosis (pressure 80-120 mm. Hg), and 24 had severe stenosis (pressure over 120 mm. Hg). Forty additional comparable records from published reports were studied.

Evaluation of several electrocardiographic abnormalities was found more informative than use of only 1. Successive increments (20-30 mm. Hg) of right ventricular systolic pressure were associated with additional electrocardiographic abnormalities unusual in patients with milder degrees of obstruction. Signs of right ventricular hypertrophy merging into "strain" were ranked in order of increasing selectivity for detecting severity of stenosis. Right axis deviation, predominant R in aV_R and V_1 or V_{3R} occurred with mild stenosis. Predominant SV_6 and amplitude of RV_1 or V_{3R} of 11-30 mm. indicated moderate stenosis. Amplitude of RV_1 or V_{3R} greater than 30 mm., displacement of transitional zone to $V_{5\text{-}6}$, high-peaked P waves, and deep inversion of T in III, aV_F, and precordial leads through V_4 were found in severe stenosis. Exceptions occurred so infrequently that we believe careful analysis of the electrocardiogram is useful for classification of degree of obstruction in patients with isolated pulmonic stenosis.

Blood Coagulation Following Myocardial Infarction

George E. Ennis, Chapel Hill, N. C.

A study was undertaken to determine whether hypercoagulation is present immediately following acute myocardial infarction. Three tests were selected: whole blood clotting time in siliconized glassware; one-stage prothrombin time; and partial thromboplastin time. Eighteen patients were found suitable for inclusion, and each was paired with a normal control. There were 10 males, ranging in age from 38 to 75 years, and 8 females, ranging in age from 58 to 82 years.

1. *Whole blood clotting time.* In 14 pairs (78 per cent), the patients had the shorter clotting time, with differences ranging from 1 to 17 minutes. The total difference was 113 minutes, with an average difference of 6.3 minutes.

2. *One-stage prothrombin time.* The patients had the shorter prothrombin time in 12 of the 18 pairs (67 per cent). The total difference was 7.8 seconds, with an average difference of 0.4 seconds.

3. *Partial thromboplastin time.* This was determined on 14 of the 18 pairs. The patients had the shorter time in 11 of the pairs (79 per cent). The total difference was 88.5 seconds, with an average difference of 6.3 seconds.

Statistically these differences are significant for the whole blood clotting time and the partial thromboplastin time. The prothrombin time shows a trend toward hypercoagulation, but is not as impressive. What constitutes an important difference as far as each patient is concerned is not known.

Estimation of Changes in Skin and Muscle Circulations Using Intraarterial RISA

Frank J. Fedor and Edward D. Freis, Washington, D. C.

Separate scintillation counters were placed adjacent to the calf and sole of the foot. I^{131} transit curves following intra-arterial RISA were obtained on direct writing recorders with the extremity at rest, after exercise of calf muscles and after intra-arterial injections of medications in 28 individuals.

Various parameters of the curves were studied for suitability as approximate indices of local blood flow: *area* and *peak height* decreased with generalized dilation of the extremity (isotope dilution) and increased with localized dilation (diversion to the area). *Appearance time* decreased with local dilation but also was shortened in other areas of the extremity. Hence, none of these could be used as indices of flow. However, *downslope gradient* increased (steepened) whether dilation was local or generalized and reflected the degree of hyperc-

mi[illegible] Thus, flow primarily rather than volume see[illegible]ed to determine downslope gradient in the extre[illegible]ity.

[illegible]ntrol calf downslope gradients averaged 13° in [illegible]ormal subjects. Local exercise increased the gr[illegible]ient 5 fold and Arlidin 4 fold in the calf, but no[illegible] in the foot. The increased calf gradient was no[illegible] prevented by epinephrine iontophoresed locally or [illegible]y exposure in a cold room suggesting that the cal[illegible] dilation was primarily in the muscle. Alth[illegible]gh Priscoline or Dibenzylene increased the gr[illegible]ient in the calf 2 to 4 fold, it also increased it in [illegible]he foot 7 to 16 fold. These increases were inhil[illegible]ted in a cold room suggesting dilation primarily in [illegible]he skin.

This method is simple if equipment is available. Pr[illegible]liminary results suggest possible clinical usefulness.

Abnormalities of the Arterial Pulse Wave in Young Diabetic Subjects

Arthur W. Feinberg, Great Neck, N. Y., and Henry Lax, New York, N. Y.

Abnormalities have been noted in the arterial pulse wave, recorded with a new technic from the digits of human subjects, in patients with peripheral arteriosclerosis and with hypertension. The major change noted is diminution to disappearance of the dicrotic wave. The accuracy of the recordings has been demonstrated by the similarity of simultaneous intra-arterial and peri-arterial tracings.

This abnormality has also been found in young diabetic patients. Thirty-one diabetic subjects between the ages of 10 and 29 were examined. Twenty-two (67 per cent) had abnormal arterial pulse waves, although none had clinical evidence of arteriosclerosis or hypertension. Only 3 abnormal cases (8 per cent) were found in a control group of 35 nondiabetic subjects. No correlation was established between the severity of the diabetes, as measured by insulin requirements, and the presence of an abnormal arterial pulse wave. The longer the duration of diabetes, the more likely pulse wave configurations would be abnormal. Although the median age was similar in the 2 groups, only 6 of 13 (45 per cent) patients who had had diabetes less than 5 years showed abnormalities, whereas 16 of 18 subjects (88 per cent) who had the disease longer than 5 years had abnormal recordings. Even of 21 additional control subjects with a positive family history of diabetes had abnormal pulse waves, although nondiabetic themselves.

This technic seems to offer a means of detecting changes in the arterial pulse wave configurations of young diabetic patients, and in nondiabetic subjects with a positive family history of the disease that antedates clinical evidence of change in their vascular system.

Estimation of Cardiac Oxygen Consumption from the Product of Heart Rate and Mean Blood Pressure

Harold Feinberg, Augusto Gerola, and Louis N. Katz, Chicago, Ill.*

Cardiac oxygen consumption determinations require the measurement of coronary flow and of coronary arteriovenous oxygen difference. The only practical means of obtaining such measurements in man (and the intact animal) involve catheterization of the coronary sinus, a procedure fraught with difficulty and by no means free of significant error.

In connection with recent studies of the oxygen cost of the cardiac performance, it was found that the product—mean blood pressure (BP) times heart rate (HR)—bears a fairly constant relationship to the myocardial oxygen consumption in the open-chested dog preparation. Hypoxia and hypercapnia have little influence on this relationship, while catecholamines have a definite though variable effect. Thus far, it appears that the product HR × BP provides a better basis for the prediction of cardiac oxygen consumption than does the cardiac external work, calculated as the product of the minute cardiac output and the mean blood pressure. Further, as the coronary A-V oxygen difference is relatively constant despite wide variations in cardiac performance, the coronary flow is adjusted closely to the varying cardiac oxygen consumption. Thus, subject to the modifying effect of the arterial blood oxygen and carbon dioxide levels and that of catecholamines on coronary A-V oxygen difference, a prediction of the cardiac oxygen consumption based on the HR × BP index may also provide a means for a qualitative estimate of coronary flow. The use of the product HR ×BP may thus prove of value for the clinical appraisal of the important physiologic variables, cardiac oxygen consumption and coronary flow.

Prognostic Significance of Rheumatic Valvulitis

Alvan R. Feinstein, New York, N. Y., and Rodolfo Di Massa, Irvington-on-Hudson, N. Y.

Features of the acute rheumatic fever attack were analyzed and correlated with subsequent cardiac residual damage in 324 children and adolescents without previous heart disease, who were followed at monthly intervals for an average of 5.3 years. They received continuous antimicrobial agents to prevent recurrences of rheumatic fever.

The patients were classified according to the murmurs present during the acute attack, regardless of coexisting features of "carditis." The

designation "valvulitis" was given to 115 patients in whom a definite diastolic murmur was present during the acute attack. Of these patients, 83 (72 per cent) have heart disease today. The designation "probable valvulitis" was given to those patients without a diastolic murmur who developed: (1) a long systolic murmur, loudest at the apex and radiating to the left axilla, or (2) a questionable diastolic murmur. Of the 45 patients in this category, 10 (22 per cent) have heart disease today.

The designation "no valvulitis" was given to those patients who failed to meet the above criteria for valvular involvement, although most of these patients had other systolic murmurs and many had prolonged PR intervals, tachycardia and gallop rhythm. Of the 164 patients in this group, none has heart disease today.

The existing data strongly suggest that patients with rheumatic fever who do not fill these criteria for valvular involvement may be reasonably reassured that heart disease will not follow the attack. The data also indicate the importance of auscultation as a diagnostic instrument.

Unheard Diastolic Murmur: An Important Feature in the Development of Rheumatic Heart Disease

Alvan R. Feinstein, New York, N. Y., and Rodolfo Di Massa, Irvington-on-Hudson, N. Y.

Acute rheumatic carditis can produce characteristic diastolic murmurs which appear (1) in early diastole at the left sternal border or base or (2) in mid-diastole, at the apex, in association with a systolic murmur. The present work reports the frequency with which these murmurs occur and are not noted.

The features of the acute rheumatic attack were analyzed in 324 patients, without pre-existing heart disease, who had been sent to Irvington House for acute or convalescent care. In 209 patients, no diastolic murmurs appeared. In 11, diastolic murmurs developed at some time after admission to Irvington House. The remaining 104 patients comprise the major material of the present report. In 72 of this group, diastolic murmurs had been noted *before* the patient came to Irvington House; 39 of these patients came from teaching hospitals; 33 came from nonteaching sources. The other 32 patients were found to have diastolic murmurs *on admission* to Irvington House. Since the patients were transferred directly and since the referring records were carefully reviewed, it must be assumed that the murmurs had been present previously but had not been noted. In this group of patients, 4 came from teaching hospitals and 28 from nonteaching sources. When diastolic murmurs were present, they had thus been unheard in 10 per cent (4/41) of patients from teaching sources and in 46 per cent (28/61) of those from nonteaching sources.

Unheard diastolic murmurs may be "discovered" at subsequent examinations and considered to be new developments. They may then be erroneously attributed to progressive valvular scarring, rheumatic activity, SBE or other pathologic processes. The existence of the unheard murmur phenomenon should be considered in evaluating results of follow-up studies where "new" murmurs are a crucial feature of the data.

Evaluation of Chlorothiazide Alone in the Treatment of Moderately Severe and Severe Hypertension

Frank A. Finnerty, Jr.,‡ Joachim H. Buchholz, John Tuckman, and George T. Hajjar, Washington, D. C.

Although studies in many clinics have demonstrated the potentiation of antihypertensive agents by chlorothiazide, the value of chlorothiazide alone in patients with moderately severe and severe hypertension has not been established. The present investigation was designed to compare the effectiveness of alternate 6-month courses of chlorothiazide alone with standard antihypertensive therapy in 34 patients. A 1-month period of no therapy was also included in the study. All patients received chlorothiazide in a dosage of 500 mg. twice daily. During the period of standard therapy, the 10 patients with severe hypertension (grade III and IV fundi) received mecamylamine plus reserpine and the 24 patients with moderately severe hypertension (grade II fundi) received either hydralazine plus reserpine or veratrum plus reserpine. The daily dose of reserpine was 0.25 mg. The dosages of mecamylamine, hydralazine and veratrum were individualized.

The average mean arterial pressure in the 10 patients with severe hypertension during the no treatment period was 168 ± 32 mm. Hg; during the period of standard therapy it was 152 ± 14 mm. Hg and during the chlorothiazide period it was 159 ± 15 mm. Hg. The average mean arterial pressure in the 24 patients with moderately severe hypertension during the no treatment period was 155 ± 26 mm. Hg, during the period of standard therapy it was 150 ± 18 mm. Hg and during the chlorothiazide period was 145 ± 20 mm. Hg. Chlorothiazide alone did not produce more than a 20 mm. Hg reduction in mean arterial pressure in any patient in the severe group. In the moderately severe group, a satisfactory therapeutic response (20 mm. Hg reduction in mean arterial pressure with relief of symptoms without toxicity) was noted in only 6 of the 24 patients. Five

patients demonstrated this satisfactory response to both chlorothiazide alone and hydralazine plus reserpine, whereas 1 patient responded only to hydralazine plus reserpine.

It is concluded from these studies (1) that neither chlorothiazide alone nor standard therapy is effective in severe hypertension, and (2) that chlorothiazide alone can be substituted for hydralazine plus reserpine in 20 per cent of patients with moderately severe hypertension.

Changes in Heart Rate During Levarterenol Infusion: Index of Arterial Elasticity

Frank A. Finnerty, Jr.,† George T. Hajjar, and John Tuckman, Washington, D. C.

Studies in this laboratory have demonstrated varying responses in heart rate during levarterenol induced hypertension in different disease states and that these changes in heart rate are not dependent on either the control level of arterial pressure or the percentage increase in mean arterial pressure. A 38 per cent average increase in mean arterial pressure in 44 young patients without cardiovascular disease was associated with an average reduction in heart rate from 79.9 ± 14 to 58.3 ± 13 beats per minute (a 25 per cent reduction). A 35 per cent average increase in mean arterial pressure in 11 patients with an elevated arterial pressure without obvious signs of sclerosis was accompanied by a reduction in heart rate from an average of 81.3 ± 11 to 59.0 ± 10 beats per minute (a 27 per cent reduction). A 44 per cent average increase in mean arterial pressure in 15 patients with toxemia of pregnancy was accompanied by a reduction in heart rate from an average of 87.8 ± 4 to 69.5 ± 6 beats per minute (a 21 per cent reduction). On the other hand, a 39 per cent average increase in mean arterial pressure in 12 patients who showed evidence of both hypertension and sclerosis was associated with no significant change in heart rate (71.9 ± 13 to 71.4 ± 12 beats per minute, a 0.5 per cent change). A 52 per cent average increase in mean arterial pressure in 12 arteriosclerotic patients with normal arterial pressure was associated with no significant change in heart rate (77.0 ± 14 to 75.0 ± 14 beats per minute, a 3 per cent reduction).

It is postulated that the differentiating feature deciding whether levarterenol produces bradycardia or not is the elasticity of the aorta and carotid sinus. It seems, therefore, that changes in heart rate during levarterenol infusion might be used as an index of aortic elasticity; uncovering these large vessel changes thus enables differentiation between diseases characterized by vasospasm and large vessel pathology.

Effect of Potassium and Digitalis on Atrioventricular (A-V) Conduction in Atrial Fibrillation

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In a study of the relation between K and digitalis, K was administered to 4 groups of individuals with atrial fibrillation. This arrhythmia was chosen because: (1) it was easier to determine the "degree" of digitalization than in the presence of sinus rhythm, (2) K administered to a "fully" digitalized patient with atrial fibrillation should, by its "antagonism" to digitalis, improve conduction via the A-V node and increase ventricular rate. Aqueous isotonic KCl or phosphate in doses of .5 mEq. per Kg., was administered intravenously in 10-60 minutes. At least one period (2.4 min.) of rapid infusion (10 ml. per minute) was recorded during each experiment. EKG's were taken continuously during rapid infusion and every 5-10 minutes during the remainder of the experiment.

Group I consisted of 20 patients fully digitalized, as shown by failure to speed the rate with i.v. atropine (2.0 mg.), appearance of A-V nodal escape beats and in some ventricular ectopic beats. Intravenous K caused further depression of conduction with slowing of ventricular rate in 4 and appearance of complete A-V dissociation in 12. Termination of injection was heralded by prompt reappearance of preinfusion rate and rhythm.

Group II consisted of 18 patients who were not digitalized. K had no depressing effect on A-V conduction.

Group III consisted of 10 patients who received 2 or more infusions of K during various stages of digitalization. The results were the same as in groups I and II, depending on degree of digitalization.

Group IV consisted of 17 patients fully digitalized but who, in addition, were given 2.0 mg. of atropine. K after atropine caused some slowing of the ventricular rate by the A-V nodal escape beats and A-V dissociation could not be reproduced.

This study failed to demonstrate the expected digitalis and potassium "antagonism," but on the other hand suggested an "additive" effect of the two. Since the depression of A-V conduction became evident only after full digitalization, further study may prove the usefulness of rapid (10 ml. per minute) administration of isotonic K for 2-3 minutes as a test for digitalization.

Ocular Fundi in Diastolic Hypertension

Max W. Fischbach, Philadelphia, Pa.

One hundred patients in whom retinal changes and cardiovascular renal disease were correlated were observed for 5 to 10 years.

A critical consideration of the usual (Keith-Wagner) gradation of angiopathy revealed that signs considered irreversible disappeared when diastolic hypertension was ameliorated. Likewise hemorrhages and exudates were commonly transient and invalidated a rigid classification with prognostic implications from a single examination.

Secondary diastolic hypertension was associated with significantly milder angiopathy than essential hypertension. Periarteritis nodosa was the exception.

Angiospastic retinopathy with a benign clinical course predominated in hypertensive females except in diabetics, and some males with similar retinal findings shared this fate; but most males had a lesser degree of diastolic hypertension, pronounced hyperplastic changes in the retinal vessels, and an earlier incidence of coronary thrombosis and cerebral vascular accidents.

Hypertensive retinal angiopathy was diagnostic in 12 per cent of the patients who were normotensive because of debilitating disease, pyrexia, etc. Retinopathy correlated more closely with morbidity and mortality than angiopathy alone—except in diabetics.

Hypertensive retinal angiopathy is pathognomonic of hypertensive vascular disease. There is, however, a distinctive difference between hypertensive and nonhypertensive retinal angiopathy. The essential difference is constriction.

Response of Infants with Large Ventricular Septal Defects to Banding of the Pulmonary Artery

Richard L. Fowler, Harold M. Albert, Rosalind Novick, Francis A. Puyau, and Claude C. Craighead, New Orleans, La.

Nine infants with intractable cardiac failure due to ventricular septal defects or physiologically similar lesions treated by temporary banding of the pulmonary artery form the subject of this report. Further study of this procedure appears justified by the current formidable mortality rates associated with attempts to close such defects by open-heart surgery in the age group under study. The relatively high mortality rate of the original study was probably related both to choice of patients and to relatively complicated surgical technic. The present series consists entirely of young infants desperately ill with intractable cardiac failure and/or severe pulmonary hypertension. The infants were studied before, during, and after surgery to determine their physiologic responses.

The surgical technic utilized consisted of passing an umbilical tape band around the main pulmonary artery in the region of the annulus and slowly constricting it until a change in the pulmonary pressure curve occurred, including preferably production of a gradient. Eight of the 9 children so treated survived and were considerably improved as demonstrated by return of growth curve to normal, alleviation of cardiac failure, and striking improvement in general strength and vigor. Postoperative catheterization studies showed a further decline in pulmonary pressure, although a left-to-right shunt usually persisted. Reversal of shunt could usually be demonstrated during exercise by the appearance of arterial desaturation. It is concluded that pulmonary banding is an effective and comparatively safe method of tiding severely ill children over the critical period of infancy to a point where definitive surgery is more likely to be successful.

Comparison of the Differential Pressure Catheter-Computer Technic with Other Methods for the Measurement of Instantaneous Pulsatile Blood Velocity

Samuel M. Fox, III, Alexander J. Mallos, Theodore Cooper, and Donald L. Fry, Bethesda, Md.

The measurement of instantaneous blood velocity affords a more sensitive indication of certain dynamic functions of the heart and vascular tree than mean flow determinations. The catheter-computer technic appears to offer the first practical method of obtaining these measurements in man. It is the purpose of this report: (1) to evaluate the validity of this method, and (2) to describe velocity contours obtained under various conditions and at various locations in dogs and man.

The validity was tested by comparing the velocity pulse curves obtained with those derived from 2 other velocity measuring systems. Close correspondence of contours was obtained when the technic was used simultaneously with an electromagnetic flowmeter placed in the thoracic aorta of dogs.

The mean deviation of the mean ordinate values forming the velocity curves agreed within 10 per cent with those obtained from an electronically monitored piston flow-generator.

Dogs with acutely produced aortic valvular insufficiency and aortic root shunts were found to have significant changes in velocity contour, including phases of early diastolic backflow from the thoracic aorta.

Equally striking were the changes in velocity curves at different aortic levels in normal dogs and the alterations produced by inotropic and vasoactive drugs. The chief difficulties encountered were connected with maintaining an adequate pressure transmitting system and in the detection of times of zero flow.

The application of the technic, using a no. 6 double-lumen catheter in the unanesthetized intact human, has given informative velocity contours of physiologic significance.

Responses of the Pulmonary and Systemic Circulations in Man to Acute Alterations of Alveolar Carbon Dioxide Tension

Charles W. Frank, Alphonzo Jordan, Fredo Kaufhaber, and Myron Zinn, New York, N. Y.

Certain hemodynamic responses to an acute increase in the alveolar carbon dioxide tension were investigated in 36 patients with rheumatic heart disease. The inhalation of 3 or 5 per cent CO_2 in air resulted in a prompt, consistent, and often impressive elevation of the pulmonary arterial blood pressure. The magnitude of the pressor response was related to the control level of pulmonary arterial pressure, and the degree of acidosis induced.

The cardiac output varied little, and the changes when present did not correlate with the increases in pressure. (Fick principle after 20-40 minutes of breathing gas mixtures.) In 3 subjects, the rise in pulmonary artery pressure was greater while breathing CO_2 at rest than during light exercise breathing air, despite a higher cardiac output in each case during exercise.

Hyperpnea per se cannot account for the pressure rise since: 1. Voluntary hyperventilation breathing air caused no rise in pulmonary arterial pressure. 2. Voluntary continuation of CO_2 induced hyperpnea after the inspired mixture was switched from CO_2 to air resulted in a prompt fall of pulmonary arterial pressures. 3. The mean intraesophageal pressure fell slightly during the period of CO_2-induced pulmonary hypertension. 4. Two subjects were studied during general anesthesia with complete muscular paralysis (succinyl choline chloride) and controlled positive pressure ventilation. Pulmonary hypertension developed in each case when carbon dioxide was added to the inspired mixture, although the control pattern of ventilation was maintained unchanged.

Reactive Hyperemia Test in the Management of Patients with Peripheral Vascular Disease

Norman E. Freeman, Rutherford S. Gilfillan, Frank H. Leeds, San Francisco, Calif., Helio M. Coelho, San Paulo, Brazil, and Gerald J. Nicholson, San Francisco, Calif.

We have developed the so-called reactive hyperemia test which measures quantitatively the filling pressure in the small vessels of the human extremity. By this test, the feet are elevated to 60 cm. above heart level, kept there for 2 minutes and then blood pressure cuffs, placed about the ankles, are inflated for a period of 5 minutes. After release of the pressure in the cuffs, the filling of the blood vessels can be observed readily by watching the color of the soles of the feet and toes. The distance in centimeters above heart level at which filling is complete is the end point. This test has been used over a period of 7 years and we have found it to be reliable and useful in the diagnosis and prognosis in cases of obliterative arterial disease and as a guide to therapy.

In patients with rest pain or ischemic lesions of the toes or feet, the critical filling pressure appears to be about 35 cm. above heart level. If the pressure is above this figure, conservative treatment or local amputations are generally successful. Below this level, healing will not take place, with rare exceptions. The progress of the arterial disease or recovery through the development of collateral circulation can be accurately followed. The effect of the administration of vasodilator drugs, sympathectomy or direct surgery on the involved arteries can be evaluated.

Linear Vectorcardiogram and its Practical Value in Vectorcardiographic and Electrocardiographic Interpretation

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A planar vectorcardiogram consists of a tracing of a point of light on an oscilloscopic screen emanating from a zero potential (E-point) producing 3 loops representing the varying magnitudes and directions in each of the P, QRS and T vectors generated during the cardiac cycle and projected on any body plane of reference. The E-point is often very unstable and interferes with the recording of the vectorcardiogram, especially for events occurring at or near the E-point. The linear vectorcardiogram is produced by moving the point source of light in a straight line, thus separating the P, QRS and T events on the screen each separated by P-R, RS-T and T-P segments respectively. This linear record clearly shows all the characteristics of the planar vectorcardiogram even in the presence of an unstable E-point. This information may now be readily utilized in visualizing the exact configuration and timing of the events in the planar vectorcardiogram, and because of its resemblance to the electrocardiogram the linear vectorcardiogram facilitates correlation of the events shown in the electrocardiogram and its corresponding planar vectorcardiograms.

Association of a Specific Behavior Pattern with Increases in Blood Cholesterol, Blood Clotting Time and Incidence of Clinical Coronary Disease

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The possible causal role of socio-economic pressure and stress in the pathogenesis of coronary

disease was studied by controlled selection and investigation of 3 groups of men (ages 30-60 years) exhibiting different overt behavior patterns. Men of Group A (83) exhibited a behavior pattern indicative of intense ambition, competitive drive, sense of urgency and preoccupation with "deadlines." Men of Group B (83) exhibited a converse behavior pattern. Men of Group C (46) being blind and unemployed exhibited a behavior pattern suggestive of simple anxiety.

Blood cholesterol, blood clotting time and a precise assay of dietary, drinking and exercise habits were obtained. Also the possible presence of clinical coronary disease was determined.

Total caloric and fat intake (± 2,000 calories and 46 per cent respectively) and amount of physical activity were approximately the same in all groups. However, average blood cholesterol in Group A (255 mg. per cent) was significantly higher than that of Group B (218 mg. per cent) and Group C (219 mg. per cent). Clotting time also was fastest in Group A.

Far more striking, however, was the startling difference in observed incidence of clinical coronary disease itself. Its over-all incidence was 27.8 per cent in Group A, a value approximately 8 times that found in Group B (3.6 per cent), and 6 times that found in Group C (4.4 per cent).

These findings suggest that a specific type of overt behavior pattern (in contradistinction to a neurosis) may specifically elevate blood cholesterol, hasten clotting and more important, induce coronary disease itself.

Sodium Gradient and Blood Pressure Regulation

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Using rat colon strips in vitro, it can be shown that the acute reduction of sodium in the medium (Na_o) results in an increase in tension, which passes off as equilibration follows. Such contraction is proportional to the degree of fall in Na_o and may be aborted by the acute addition of sodium to the medium. Drug induced contraction operates similarly, since it too can be interrupted by the addition of sodium to the medium. This also applies to the vascular smooth muscle in the whole animal. Thus, drug-induced pressor responses are associated with a fall in extracellular Na (Na_o) and can be interrupted by the acute infusion of sodium.

After equilibration of the colon strip in a high sodium medium, the responsiveness to contraction inducing procedures is reduced and similarly an infusion of sodium in the whole animal reduces vascular responsiveness to pressor agents. These effects are consistent with the view that the concentration gradient Na_o/Na_i is causally and inversely related to smooth muscle tension (diastolic pressure). Acute changes in tension may result from rapid transfers of sodium between the two phases, while chronic changes probably reflect a basic shift in equilibrium favoring either an increase or decrease in Na_i. We suggest that in chronic situations, Na_o changes are subsequent attempts at compensation. This is supported by the fact that although, as is well known, the chronic administration of sodium accelerates DCA hypertension (presumably by accelerating the rate of Na_i accumulation) the acute infusion of sodium dramatically reduces it.

Antifibrillatory Agents and Surgical Revascularizing Procedures Tested by Acute Closed-Chest Coronary Occlusion in the Pig

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To minimize the influence of the open chest, premedication and anesthesia upon experimental coronary occlusion, an accurate technic of closed-chest coronary artery occlusion has been developed. The method employs a teflon snare enclosed in a flexible cable. This is attached to a plastic platform which overrides the artery to be occluded. Two to 4 hours following installation of this apparatus, permitting recovery of the animal, external control provides acute 1-stage coronary artery occlusion. All studies were monitored by the electrocardiogram. Because of the similarity between the normal human heart and the pig heart, the pig has been used as the experimental test animal. Antifibrillatory agents and surgical revascularizing procedures have been tested in 142 pigs. The results have been as follows:

Forty-two control, untreated animals died of ventricular fibrillation, two-thirds dying within 5 minutes. The longest survival time in this group was 27½ minutes. Eighteen animals were pretreated with 2,6-Bis (1-piperidylmethyl)-4(2,2-dimethylbenzyl) phenol dihydromide. Eight survived. Thirty animals were pretreated with Pronestyl. One survived. On 18 animals, the Beck no. 1 operation was performed, and 5 of these survived following acute closed-chest coronary occlusion 60 to 90 days later. On 10 pigs acute internal mammary ligation was followed by acute closed-chest coronary occlusion during the same day. None survived. Ten animals with chronic internal mammary ligation were challenged 30 to 60 days later. Three survived.

All chronic survivors developed myocardial infarcts in the area served by the occluded left anterior descending branch.

Newer Concepts of Bioenergetics in Experimental Congestive Heart Failure

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Congestive heart failure (CHF) has been produced in the guinea pig by surgical means. This experimental CHF has been shown to involve sequentially the left ventricle and atrium, the lungs, the right ventricle and atrium, liver and other organs.

Mitochondrial systems derived from the heart and liver, in both normal and CHF animals, were studied as follows: 1) the efficiency of phosphorylation in relation to oxidation (P/O ratio); 2) oxidation per hour, per milligram of nitrogen, ($Q^N_{O_2}$) value; 3) use of inhibitors, such as malonate.

It was demonstrated that the P/O ratios with α-ketoglutarate or glutamate as substrates were within the normal range for the CHF animals in both the liver and heart mitochondrial systems. The $Q^N_{O_2}$ values for liver and heart in the CHF group were lower than in the normal group.

The addition of malonate to the heart and liver mitochondrial systems from the CHF animals with α-ketoglutarate as the substrate had striking results. The $Q^N_{O_2}$ value compared to normal animals is depressed 60 and 90 per cent in the liver and heart respectively. The P/O ratios could not be calculated. The malonate inhibitory effect on the $Q^N_{O_2}$ value could be reversed in both the liver and heart mitochondrial systems by the addition of certain combinations of cofactors. Although the coenzymes restored the $Q^N_{O_2}$ values, phosphorylation remained depressed, indicating either that irreversible damage was done to the energy yielding process by malonate in CHF mitochondrial or that additional factors may have to be added for its restoration.

Mitral Insufficiency: Clinical and Hemodynamic Studies Following Direct Vision Surgical Correction

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Rheumatic mitral insufficiency may be the major cause of progressive cardiac enlargement, heart failure and death in children as well as in adults. With a pump oxygenator and direct vision surgical technics, significant and sustained reductions in regurgitant flow can be achieved.

Five patients, ranging in age from 7 to 25 years, were observed medically for 1 to 4 years. Increasing cardiomegaly and heart failure were the indications for surgery.

Four patients had intractable heart failure prior to surgery; 2 had uncontrolled auricular fibrillation, and a third, a 7-year-old girl, had had massive collapse of the left lung for 2 months. Preoperative pulmonary artery pressures varied from 52/18 to 125/50 mm. Hg with elevations of left atrial pressure to from 17 to 33 mm. Hg mean.

At operation, annular dilation was the major structural lesion, and in all mitral annuloplasty was performed. Reductions in regurgitant flow and falls in left atrial pressure were achieved.

In 3 patients, initial clinical improvement has been sustained for 4 to 6 months. Re-expansion of the collapsed left lung and control of heart failure has been achieved in the 7-year-old girl, Five weeks postoperatively, the pulmonary artery pressure in another 7-year-old girl had fallen to 85/46 mm. Hg from a preoperative level of 128/58 mm. Hg. One patient died 24 hours after surgery from hemorrhage. The heart failure status of the remaining patient, an 8-year-old boy, has been unchanged; active rheumatic fever is suspected in this patient.

Electrocardiographic Changes in Asian Influenza

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To ascertain the incidence of significant electrocardiographic changes in patients with Asian influenza, adult male students, ages 18-28, were investigated. They comprised successive admissions to the student infirmary in whom the diagnosis of Asian influenza had been made clinically, and were unselected as regards the severity of their illness. None was found on examination to have clinical evidence of cardiovascular involvement. Standard 12-lead electrocardiograms were taken on admission and on alternate days during hospitalization. A later electrocardiogram was taken 1-4 months after discharge. The clinical diagnosis of Asian influenza was confirmed by serologic tests in 86 of 101 patients, and only these 86 were considered. For analysis of the electrocardiographic findings, a control series of 150 healthy adult males in the same age group was used.

During illness there was no significant abnormality of heart rate or rhythm. The P-R interval was normal, but the Q-Tc time was significantly diminished in the initial tracings. In 9 patients S-T and T wave changes occurred, either in the initial or final tracings, which exceeded the limits of normality as assessed from the control group. Taking all patients as a group, there was a statistically significant depression of T waves in the initial tracings as compared with the final tracings,

the latter being comparable to the normal controls.

Conclusion: Minor electrocardiographic changes did take place in a small proportion of patients with Asian influenza. There was, however, no clinical evidence of cardiovascular disease.

Physiologic Study of the Chemoreceptor Mechanism in the Dog at Sea Level and at High Altitude (12,600 ft.).

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After evaluation of various methods of denervation of the canine aortic and carotid chemoreceptors, the following method was adopted. The aortic arch and adjacent portions of the supra-aortic branches were dissected free of all adjacent tissues from the level of the left subclavian artery to the coronary sinus. The carotid bifurcation was exposed unilaterally and dissected free including the sinus. The occipital artery was ligated flush with the wall of the external carotid and a segment of the occipital artery, attached carotid body and adjacent tissue were removed. The contralateral carotid artery was prepared at a separate procedure under light Nembutol or chloralose anesthesia since respiratory failure was a major problem following complete ablation of the chemoreceptors and denervation of these areas.

The respiratory physiology, blood volume, and vasomotor activity were studied without anesthesia. At high altitude, the red cell mass in acclimatized dogs showed a marked increase over the controls. There was a markedly decreased respiratory sensitivity to hypoxia. The sensitivity to carbon dioxide failed to show the normal increase on acclimatization. Plethysmographic study of spontaneous vasomotor activity showed alpha waves to be present in the forepaw of the prepared animals, indicating that the denervated area was not their source.

New Antihypertensive Drug, 1-Phenyl-2-Hydrazinopropane

Louis Gillespie, Jr., Luther L. Terry, and Albert Sjoerdsma, Bethesda, Md.

Recent studies in this laboratory have been designed to correlate changes in the metabolism of vasoactive monoamines such as serotonin and norepinephrine with alterations in blood pressure. It was found that a monoamine oxidase inhibitor, 1-phenyl-2-hydrazinopropane, markedly lowered the blood pressure in severe hypertensives.

The drug was administered to a small group of hospitalized hypertensive subjects in single oral doses of 12.5 to 50 mg. daily for 12 to 25 days. Significant lowering of the blood pressure was noted in each case, the predominant effect being on the standing pressure. The range of maximal decreases in standing pressure was 57-108/44-68 mm. Hg. Maximal effects were apparent within the first 10 days of therapy, and the standing pressures returned to control levels 7 to 14 days after stopping therapy. A larger group of outpatients have been maintained on 6.25 to 25 mg. of the drug per day for at least 2 months. Satisfactory control of blood pressures was achieved in every case, using this agent alone or in combination with chlorothiazide.

Although this drug effectively inhibits monoamine oxidase in man, it has not been proved that this action is responsible for the hypotensive effects. The absence of undesirable side effects warrants further trials of this agent in the management of hypertension.

Further Studies on the Cardiac Distribution of Isotopic Magnesium

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Studies of the tissue distribution of intravenously administered isotopic magnesium (magnesium[28] half life 21.3 hours) have shown that the heart has a particular avidity for this material. A further extension of this work has shown that there is a statistically valid difference in the distribution of Mg^{28} in different portions of the ventricles of dogs and rabbits. The concentration of Mg^{28} per gram of dry weight is highest in the ventricular septum, followed in order, by the left ventricle and right ventricle.

In order to determine whether these consistent concentration differences of Mg^{28} in different portions of the ventricles were related to the conduction system, studies were carried out in young calves from which the Purkinje system is easily removed at autopsy.

Proper doses of Mg^{28} were administered intravenously to 2 calves. The animals were killed at 1¼ and 3 hours following administration of isotope. The hearts were immediately removed and the ventricles laid open. The Purkinje system from the A-V node to its smallest ramification was carefully dissected from the underlying muscle. Samples of the underlying septum, right and left ventricles were also taken for assay of radioactivity. All samples were dried to constant weight and then counted. In 1 animal the usual distribution gradients were found; however, in neither animal did the highly differentiated conducting tissue show a higher concentration of Mg^{28} than the underlying heart muscle.

Practical Management of Acquired Aortic Stenosis and Indications for Surgery

Albert P. Glover, Philadelphia, Pa.

Of the 4 cardiac valves, it has long been recognized that surgical intervention in aortic valvular disease presents much greater technical difficulty and that the type of pathology is least amenable to surgical correction. Surgical approaches during the past 8 years have vacillated between the transventricular and direct aortic methods. Hypothermia and cardiac bypass have been employed.

The author has been convinced from the beginning that, until the diseased aortic valve can be removed and replaced, the best results with the lowest risk will be by the transventricular route. This series of 87 consecutive cases, operated by the transventricular route over an 8-year period, furnishes the material for this report. The first 37 patients were operated upon by an older technique with 17 operative deaths. Only 12 are alive 3 to 7 years later. The last 50 cases were done with a new relatively atraumatic technic with 3 operative deaths, and 40 are now living 6 months to 3½ years later. During the past 3 years, the operative mortality and ultimate results have exceeded all other methods of surgical intervention in aortic valve disease.

Hemodynamic data to substantiate the clinical findings and a simple classification of the stages of aortic stenosis with surgical indications have been prepared.

Paroxysmal Atrial Tachycardia with Atrioventricular Block

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Paroxysmal atrial tachycardia with atrioventricular block is a serious and frequently misdiagnosed condition. Its presence usually indicates potentially dangerous overdigitalization. Between 1954 and 1958, this arrhythmia occurred in 30 patients at the Portland Veterans Administration Hospital.

Accepted diagnostic criteria include an atrial rate of 150 to 250, altered P-wave configuration, and isoelectric baselines between atrial complexes. Seven cases with slower atrial rates (130 to 145) were included since all other criteria were satisfied. Atrioventricular block varied, but was usually 2:1 or Wenckebach in type. The ventricular rate was below 100 in half the cases, so that the arrhythmia was often unsuspected clinically.

Twenty-nine of the 30 patients had received digitalis with evidence of overdigitalization in 21. Mercurial diuretics had recently been administered to 2/3 of the group. Serious heart disease was almost universally present. Etiology varied, but striking and hitherto unreported was the frequent association of the arrhythmia with marked pulmonary disease. This was observed in 15 cases, 7 with definite cor pulmonale.

Discontinuation of digitalis and administration of potassium and procaine amide led to prompt cessation of the arrhythmia in 18 of 20 treated cases. Only once did it persist longer than 7 days.

Twenty-one patients died, often within 1 week following recognition of the arrhythmia. Death, however, was related to the underlying heart disease itself rather than to the atrial tachycardia. This itself could be regarded as detrimental only in several of the 11 cases where the ventricular rate exceeded 130.

Instrumental Technics in Correlating Heart Sounds and Murmurs with Events of the Cardiac Cycle During Combined Right and Left Heart Catheterization

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In patients with mitral and aortic valve lesions, pressures in left atrium and ventricle are obtained by consecutive atrial punctures through the bronchoscope. Needle and bronchoscope are removed, leaving one catheter in each chamber. A radiopaque vinyl plastic catheter is passed through an arterial needle to the aortic valve. Phonocardiograms are now obtained simultaneously from 2 different sites on the chest wall, together with equisensitive triple pressures and ECG.

Continuous pressure differences across stenotic valves are obtained by electronic subtraction. Simultaneous pressures are also recorded from corresponding chambers on both sides of the heart. Eight parameters may be obtained simultaneously without parallax error by an oscilloscopic recorder utilizing a single-gun tube with electron switch. Paper speeds are 50 and 150 mm. per second.

After a year's experience (75 patients) the technic has gradually evolved to the point where tracings are comparable to those previously obtained by needle puncture in the exposed heart. Accurate correlations have been made between murmurs of mitral and aortic stenosis and continuous pressure differences across the valves. The systolic murmur in 2 cases of combined aortic stenosis and insufficiency has been found to be short in duration, in keeping with the abridged ejection gradient. By reference to simultaneous aortic and pulmonary artery tracings, the components of split second sounds have been identified. The pulmonary component may be delayed in mitral stenosis, and easily mistaken for the opening snap of the mitral valve. In 1 patient it was possible to record the murmur of mitral regurgitation by transmission along the transbronchial needle.

High Energy Phosphate Metabolism in the Arrested Heart

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Canine dog hearts were arrested with potassium citrate, acetylcholine, and anoxia. Serial myocardial biopsies were taken before and during 1 hour of arrest. Using microtechnics, the muscle was analyzed for the high energy phosphates (ATP, ADP and creatine phosphate) and glycogen. In the hearts arrested with potassium citrate, the creatine phosphate (storehouse of readily available high energy phosphate) declined gradually from 8 mM per Kg. to approximately 1 mM per Kg. in about 20 minutes. The ATP declined from about 6 mM per Kg. to about 3 mM per Kg. in 1 hour. The ADP did not change substantially during the hour's arrest. The glycogen declined about 350 mg. per 100 Gm. during the period of arrest. In hearts arrested with acetylcholine, the creatine phosphate dropped to low levels in about 5 minutes and the ATP and ADP were similar to hearts arrested with potassium citrate. In hearts arrested by pure anoxia, the creatine phosphate dropped to low values in about 2 minutes. The contractions diminished markedly at this point, but the hearts continued to beat poorly for 5 minutes. In these hearts, the ATP and ADP levels were not significantly different from hearts arrested with potassium citrate. The glycogen decreased approximately 350 mg. per 100 Gm. in the anoxic arrested hearts but appeared to decrease even more rapidly in the acetylcholine arrested heart. The variability of glycogen levels in the ventricular muscle, however, makes the significance of any difference in utilization difficult to interpret.

Evidence for the Countercurrent Multiplier System for Urine Concentration

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It has been suggested that, in mammals, the urine is concentrated by diffusion of water into the interstitium of the renal medulla made hyperosmotic by a countercurrent multiplier system in the loops of Henle. Direct experimental proof has been lacking as it depends on sampling and analysis of fluid from the involved structures.

The papilla of the hamster kidney, which extends into the upper portion of the ureter, was exposed in anesthetized animals. When observed microscopically, vasa recta and collecting ducts were readily apparent. Under proper illumination, segments of narrow tubular structures filled with clear fluid were sometimes visible. These proved upon subsequent microdissection to be loops of Henle of juxtamedullary nephrons. The osmolality determined microcryoscopically of 12 samples of fluid from the bends of loops of Henle was the same, or nearly so, as fluid from adjacent collecting ducts, and higher than that of plasma from the inferior vena cava. Fluid from cortical segments of proximal tubules and late distal convolutions was isosmotic and from early distal convolutions, hypo-osmotic to plasma.

These results are consistent with the hypothesis that the mammalian nephron functions as a countercurrent multiplier system, and indicate that at no level in the kidney are there large osmotic gradients between adjacent tubular structures.

Circulation in Thyroid Disease

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A correlation of clinical and hemodynamic studies have been made in patients with myxedema or thyrotoxicosis. Although many of the symptoms and signs of the hypothyroid patients were similar to those of patients with congestive heart failure and their cardiac outputs (1.88 L. per minute per $M.^2$) were at the level of a group of patients with low output failure, the ratio of cardiac output to oxygen consumption (2.17 L. per 100 ml.) was normal at rest and during exercise as were pressures in the pulmonary circulation and right heart. In these myxedematous patients, the decreased cardiac load of hypothyroidism outweighed any decreased myocardial reserve caused by myxedema. In the patients with thyrotoxicosis without congestive failure, the cardiac output was elevated at rest and rose normally during exercise; intravascular pressures remained normal. Patients with thyrotoxicosis and clinical congestive heart failure fell into 2 groups. In 1 the cardiac output of 3.35 L. per minute per $M.^2$ was abnormally low with respect to oxygen consumption of 1.81 L. per 100 ml., and in the other the output of 8.93 L. per minute per $M.^2$ was high (4.34 L. per 100 ml.). In both groups the cardiac output failed to increase with exercise and abnormally elevated pressures were found in the right heart and lesser circulation.

These data indicate that cardiac competence or incompetence can exist at any absolute level of cardiac output, that the physiologic stigmata of congestive heart failure are similar regardless of the level of cardiac output and provide confirmation for a restatement of the relationship of cardiac reserve and circulatory load in the presence and absence of congestive failure.

Validity of Changes in Jugular Bulb Flow as Indices of Changes in Cerebral Vascular Conductance: Influence of Nicotinic Acid and Arterenol

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Cerebral venous blood flow (CBF) and jugular flow (JF) were determined simultaneously in pentobarbitalized, heparinized dogs (electromagnetic flowmeters). Cerebral venous return was isolated by occlusion of all accessible emissary veins, both internal jugular, the ophthalmic, supraorbital, angular, superficial temporal veins. The vertebral venous sinuses were injected with 20 per cent celloidin in ether acetone. The distal lateral sinuses were exposed by drill holes and occluded by packing with bone wax. Two additional drill holes were then made upstream from the first pair, and these were fitted with polyethylene needle adaptors for collection of the cerebral venous outflow.

Jugular flow was determined in the jugular bulbs, catheterized cephalad to the common facial veins. Arterenol (ART) was given in logarithmic doses from 1 to 50 μg. by way of the carotid and vertebral arteries (retrograde cannulation of brachial artery). The reduction of jugular flow was approximately the same with brachial as with carotid artery injection. Nicotinic acid (NA), 1—15 mg., was administered by the same routes. Following administration of ART, a sharp reduction in JF was apparent with only a slight decrease in CBF. With NA, the CBF was unchanged, but JF varied erratically, with reduction predominating.

Conclusion: Measurements of CBF by analysis of jugular blood may be subject to gross error which could not be detected with carotid artery injection alone but which requires tests with brachial artery injection. Neither arterenol nor nicotinic acid has any significant effect on cerebral vascular conductance.

Cinefluorographic Study of the Relation of the Left Auricle to the Barium-Filled Esophagus

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Previous reports have detailed the technical aspects of obtaining 35 mm. motion pictures of a fluoroscopic screen image from an area of 8 × 8 inches to 14.5 × 14.5 inches.

This paper is presented to demonstrate the potential value of this technic for teaching, research and clinical studies.

The relation of the left auricle to the barium-filled esophagus was chosen for this purpose. Representative films taken at 15 or 30 frames per second have been obtained from normal subjects and patients with mitral valve disease during a barium swallow in both the PA and ROA positions. Film strips from patients with mitral valve disease were selected on the basis of varying degrees of auricular enlargement, on the presence of mitral valve stenosis and/or insufficiency, and on the presence of sinus rhythm, auricular fibrillation or auricular flutter.

Carbon Monoxide Intoxication: Electrocardiographic Observations

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Though the toxic and lethal effects of carbon monoxide are well documented, there is no recorded experimental data to indicate the early toxic effects of this noxious gas on the human electrocardiogram. Under unusual atmospheric conditions, 3 garage workers lost consciousness while at work. Electrocardiographic tracings and pertinent (methemoglobin, venous oxygen and pH) chemistries were obtained within minutes after they had lost consciousness. The total period of exposure was known. Though the period of unconsciousness was brief, electrocardiograms were repeated at 48-hour intervals until the chemistries had returned to a normal level. The hazard created by unfavorable atmospheric conditions is emphasized. The toxicology, physiology, and clinical picture of carbon monoxide asphyxia has been reviewed.

Metal Concentrations in Cardiac Tissue

George C. Griffith, Balakrishna Hegde, Edward M. Butt, and Robert W. Oblath, Los Angeles, Calif.

The metallic content of cardiovascular and related tissues has been studied in the laboratories of the University of Southern California since 1949 by means of emission spectroscopy and microchemical methods. Norms for 13 trace metals in various tissues of the body were established as a preliminary to the identification and investigation of deviant patterns in disease states. Fifty-eight patients who came to necropsy were studied clinically and their hearts were assayed for trace metal content. Patients were grouped as follows: (1) acute myocardial infarction; (2) acute and chronic myocardial infarction; (3) chronic myocardial infarction; (4) coronary atherosclerosis without infarction; (5) idiopathic hypertrophy; (6) endosclerosis; (7) amyloidosis; and (8) for comparison, normals.

Metal concentrations in each ventricle and in the interventricular septum were analyzed separately. Average values for the heart as a whole were similar to values for the individual chambers

and the cardiac septum. When coronary vessels were involved in a pathologic process, sections of myocardium, including the vessels, were studied. In special instances, sections were taken from the atria, the aorta, the endocardium and/or the papillary muscles.

All hearts with low lead content were hypertrophied and flabby. Lead concentration was particularly low in the predominantly-thickened left ventricle in these patients. When areas of recent infarction were analyzed, manganese concentrations were found to be quite low; in areas containing old infarcts, manganese was elevated by comparison. Copper concentrations are high in coronary atheroselerosis. In the interventricular septum especially, copper is elevated in hearts with acute infarcts, low in hearts with chronic myocardial infarction. Apparently copper concentrations bear an inverse relationship to manganese content in these hearts. Molybdenum is present in low concentration where manganese is low, and in an inverse relationship to copper concentrations.

Metals in various diseases affecting the heart appear in definite patterns. Evidence is mounting that metals hold the key to an entirely new method of medical investigation.

Comparative Study of Two Anticoagulants (Heparin vs. Dicumarol) in Acute Complicated Myocardial Infarction

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One hundred and sixty-three patients with acute complicated myocardial infarction were assigned on hospital admission to 2 groups: 100 received concentrated aqueous heparin as sole anticoagulant (administered subcutaneously in doses of 100 to 150 mg. every 12 hours for 3 to 4 weeks); 63 were maintained on Dicumarol during their hospital stay, receiving heparin i.v. and/or i.m. in addition during the initial 2 to 4 days of hospitalization.

Comparison of the 2 groups reveals that the proportion of seriously-ill patients was much higher in the heparin group prior to treatment: the heparin group contained 29 persons (24 per cent) with 3 or more serious complications upon admission, as contrasted with only 4 (6 per cent) in the Dicumarol group. Nonetheless, gross mortality was only 28 per cent in the heparin series, as compared with 38 per cent in the Dicumarol group. Under conditions in a large general hospital, some of the patients in each group did not receive adequate anticoagulant treatment. Mortality in adequately-treated patients in the heparin group was 21 per cent; in the Dicumarol group, 31 per cent. When only patients with 3 or more complications on admission are considered, 7 patients (24 per cent) on heparin therapy died as compared with 4 patients (100 per cent) on Dicumarol therapy. This difference is statistically significant, $p = .01$.

These results demonstrate that prolonged anticoagulant treatment with concentrated aqueous heparin in acute myocardial infarction is practical, and that the mortality is lower than with use of prothrombin-depressing drugs.

Measurement of Regional Blood Flow in Dog Intestine

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A method for the measurement of capillary blood flow through the different tissues that make up a complex organ like the intestine has been devised. Glass microspheres, 20 μ in diameter and containing radiosodium, are injected into an intestinal artery. The number injected (less than 1,000) does not affect the blood flow. Barring selective separation of the spheres from blood at arterial bifurcations, they are distributed to the various tissues in proportion to the blood flow. Since the spheres are too large to pass through capillaries, they become lodged in the tissue. To determine the sphere content (and hence fractional blood flow) of each tissue, the intestine is dissected into 4 fractions: mucosa, submucosa, muscularis and mesentery, and the radioactivity of each measured. The spheres recovered in the venous drainage are a measure of arteriovenous anastamotic flow. For fasted lower ileum, the fractional capillary blood flows for mucosa, submucosa, muscularis and mesentery are 0.31, 0.28, 0.21, and 0.17, respectively. The shunt flow is 0.03. For fasted jejunum, the shunt flow is the same and the fractional flows for the tissues are 0.52, 0.20, 0.14 and 0.11, the values for mucosa and muscle being significantly different from the ileum. In the ileum, feeding increases the measured total venous outflow from 0.6 ml. per minute per Gm. to 1.0 ml. per minute per Gm., but does not alter the regional distribution. In the jejunum, feeding does not significantly change the total flow but causes a diversion of flow from the mucosa to submucosa.

Heart Disease Among Farmers: Analysis of 397 Cases with a Study of Effect on Work Output

Richard P. Gripe, Ben Z. Klatch, and Philip W. Rothrock, Lafayette, Ind.

During a 5-year study of heart disease among Indiana farmers, a stratified, random sample of 397 farmers was interviewed and examined med-

call[illegible] This consisted of a face-to-face interview by [illegible] sociologist, and a history and physical examination by a physician. Laboratory tests included an [illegible]ectrocardiogram, chest x-ray, urinalysis and blo[illegible] count.

U[illegible]ng arbitrary criteria developed in the U. S. Pul[illegible]c Health study in Framingham, Massachusett[illegible] 135 were found to have cardiovascular dis[illegible]se. Thirty-two possibly had cardiovascular disease. Two hundred twenty were found to have none. Sev[illegible]nty-seven had arteriosclerotic heart disease, 10 [illegible]d rheumatic heart disease, 23 had hypertensive heart disease, and 53 had hypertension, inclu[illegible]ng multiple diagnoses. In the "possible" gro[illegible]p, 15 had arteriosclerotic heart disease, 2 had rhe[illegible]matic heart disease, 6 had hypertensive heart dis[illegible]se, and 15 had moderate hypertension.

L[illegible]bor output of the farms was related to the hea[illegible]lh and age of the farmer. Although work output decreased with age and disease, a seemingly par[illegible]adoxical rise in output was found on farms where the operator had hypertension.

The farmer's own opinion of his health also affected work output. To the question, "Has a doctor ever said you had heart trouble?" administered as part of the Cornell Medical Index, 227 answered "Yes." Of these, 69 were found to be normal after examination. These farmers, who mistakenly believed they had heart disease, had work outputs significantly lower than other normal individuals.

Purification and Properties of Carbamyl Acetyl-Phosphatase

Santiago Grisolia,† Barbara K. Joyce, and Josefina Caravaca, Kansas City, Kans.

The carbamyl phosphate phosphatase first noticed by one of us (S.G.) in a number of animal tissues, particularly in brain, heart and skeletal muscle, has been purified about 800 times. The purified enzyme acts also upon acetylphosphate, but not on adenosine monophosphate, adenosine triphosphate and phosphoenol-pyruvate. The purified enzyme shows a single boundary in the ultracentrifuge. Although the molecular characterization is in progress, preliminary evidence indicates that this enzyme may be the smallest thus far recorded, approximately 10,000 MW. The enzyme is not destroyed by incubation with 5 M guanidine or 5 M urea; however, it is entirely destroyed by trypsin. The enzyme is markedly inhibited by thyroxine and by phosphate; magnesium, manganese, lead and ethylenediamine tetracetate did not affect the hydrolysis of carbamyl phosphate or acetylphosphate by the enzyme, while zinc, uranium, citrate and sulfate are inhibitory.

Normal Systolic Murmur

Dale Groom, Waddy Chapman, Anne Bass, Charleston, S. C., Yro T. Sihvonen, Detroit, Mich., and W. Wofford Francis, Charleston, S. C.

The presence of functional systolic murmurs in some adults has long been recognized. Of recent interest is the finding that these murmurs can actually be recorded from the precordium in virtually all normal subjects.

By means of a high-sensitivity (capacitance) pickup in a soundproof room, recordings were made on a cathode-ray oscilloscope from 71 normal adult subjects. Only those with a negative past history of a heart murmur or heart disease were included, and in none of them was a murmur audible on ordinary stethoscopic auscultation. Recordings were made with the subject at rest in the supine position.

All subjects showed readily discernible murmurs extending through one-fourth or more of systole and reproducible on repeated tracings. In more than three-fourths of the subjects the point of maximum intensity was between the second and fourth intercostal spaces along the left sternal border. Wave forms of most murmurs showed some sinusoidal characteristics with fundamental frequencies of 60-90 c.p.s. and secondary frequencies an octave or more higher. The majority of the murmurs were of decrescendo configuration following the first heart sound; only about one-third had a diamond type pattern. Their intensity tended to vary from day to day, with different phases of respiration or changes in position, and with exercise. Short diastolic murmurs followed the second heart sound in one-fourth of the subjects.

The mechanism and site of origin of these systolic sounds in the adult is uncertain. However, their presence is understandable on the basis of what is known of circulatory dynamics, and it appears that they represent a universal functional murmur which is usually subaudible.

Coronary Disease in the Negroes of Haiti and the United States

Dale Groom, Edward E. McKee, Charleston, S. C., Vergniaud Pean, Port-au-Prince, Haiti, Charles Webb, Charleston, S. C., and Faye W. Grant, Evanston, Ill.

Life of the Negro in Haiti, as compared to that of his racial brother in the United States, is characterized by privation, a meager diet, the less stressful tempo of the tropics, less sanitation and medical care, and prevalence of infections and deficiency diseases. In this relatively primitive environment, coronary disease is regarded as a rarity.

This study, based upon pathologic rather than clinical findings, is an evaluation of the degree of coronary and aortic atherosclerosis in 267 autopsy specimens. Routine autopsies, covering all types of mortality over age 20, were utilized as representative samples of the 2 population groups. All specimens were graded both grossly and microscopically on a scale of 0 to 4 by the same pathologist, their individual identity remaining unknown to him. Appropriate clinical data and detailed dietary surveys were included in this cooperative investigation.

Among the Americans there was approximately double the degree of coronary atherosclerosis (and myocardial fibrosis) in both sexes and at all age decades, while no appreciable differences were found in the corresponding aortas. Grades of male coronaries from both countries increased similarly with age to a plateau in the 40's; those of females showed a direct progression from the lowest values to the highest at 60 and beyond. Average grades in all categories were consistently lower for rural than urban subjects.

The predisposition of the American group to coronary and not to aortic atherosclerosis, a highly significant difference statistically, suggests the importance of factors other than diet in the etiology of coronary disease.

Suggested Role of Myocardial Potassium in Pathogenesis of Nocturnal Paroxysmal Dyspnea

Richard S. Gubner, New York, N. Y.

The paradoxical onset of acute left ventricular failure during sleep (cardiac asthma, nocturnal paraoxysmal dyspnea), has been attributed to factors varying from disturbing dreams to nocturnal hemodilution and increase in plasma volume. It is suggested that acute failure is not due to such factors increasing cardiac work, but to potassium induced impairment of left ventricular contractility, similar to the mechanism in the typically nocturnal attacks of familial periodic paralysis. Potassium entry into muscle is greatly augmented at night in this condition and is responsible for muscle weakness. Such potassium shifts involve the heart, as reflected by diurnal variation in T wave amplitude in the electrocardiogram.

Agents which increase skeletal and cardiac muscle potassium, such as quinidine, decrease contractility; and conversely, drugs which augment contractility, such as digitalis and adrenal steroids, lower myocardial potassium. Cardiac contractility is regulated physiologically by increased myocardial potassium efflux with increased work load, which acts as a primary servomechanism to augment contraction. With lowered work load during sleep, and minimal diurnal adrenal steroid activity, a relatively augmented intracellular/extracellular potassium ratio may develop (as occurs in skeletal muscle in familial periodic paralysis), precipitating acute cardiac failure. Increased cardiac work during the attack activates the autoregulatory potassium efflux mechanism leading to spontaneous improvement, as typically occurs.

The salutary action of diuretics in cardiac failure may in large measure be due to direct enhancement of cardiac contractility acting via decrease in myocardial electrolytes.

Extracted Heart Muscle Preparation with Respiratory and Phosphorylative Activity

Richard J. Guillory, and Wilfried F.H.M. Mommaerts,† Los Angeles, Calif.

Due to the efforts of A. Szent-Györgyi, there is now available a glycerol-extracted muscle preparation, also obtainable from cardiac muscle, which shows contraction upon the addition of adenosine triphosphate (ATP). We have observed that similar preparations, likewise with contractile properties, can be prepared with aqueous sucrose solutions. Since this procedure preserves the mitochondria, they also have oxidative activity.

The preparation worked out for respiration studies consists of small prisms, about 2 × 0.2 × 0.2 mm., cut from slices of rat heart, and extracted for various lengths of time with 0.30 M sucrose. These particles, consisting of both the fibrillar and mitochondrial systems in their normal juxtaposition, have a low intrinsic respiration, but display an O_2 consumption of the order of 200 μl. O_2 per hour per 100 mg. tissue when substrates such as succinate or α-ketoglutarate are added. Concomitant with this oxidation, they show phosphorylation of ADP, detected by trapping the ATP formed with hexokinase and glucose. The observed P:O ratios are lower than in mitochondria. This is not due to some destruction during their preparation, since normal mitochondria can be isolated from these particles afterwards. Instead we ascribe it to the ATPase activity of the fibrils.

The preparation is being used for the study of the connection between oxidation and mechanical activity in a system which is not complicated by the various physiologic factors which normally obscure this connection.

Correlation of Electric and Anatomic Positions, Using Biplane Angiocardiography and Conventional Electrocardiograms

Warren G. Guntheroth, Seattle, Wash., Carl-Olaf Ovenfors, and Danae Ikkos, Stockholm, Sweden

Anatomic diagnosis is one of the major goals in the clinical application of the electrocardio-

graph. However, literal translation of electric position to anatomic position is not warranted on the basis of data presented in published data. We have studied the anatomic and electric position of the heart in 53 children. Anatomic axis in the frontal plane, the presence and degree of septal rotation about its longitudinal axis, and the projection of the septum on the left chest wall were determined from angiocardiograms taken on an Elema machine which allows full-sized films in simultaneous anterior-posterior and true lateral projections. Patients were included only when both ventricles were filled consecutively. The outline of each ventricle were superimposed in a single drawing for each projection. The position of the conventional Wilson unipolar chest leads was determined from scout films taken on the Elema machine, in the same projections, with the electrodes in place. The mean electric axis was calculated from the standard limb leads. The transition zone and the first leads on either side of the transition zone generally regarded as characteristic of the right and left ventricles, morphologically, were determined from the chest leads. There was no significant correlation between anatomic and electric positions, nor could discrepancies be accounted for by rotation around the longitudinal axis of the septum. In fact, the septum rarely varied from a truly vertical position, and when rotation was present there was no correlation with the electrical position.

Effect of Acute Myocardial Infarction on the Intracardiac Phonocardiogram of the Intact Dog

Santiago V. Guzman, Antonio C. de Leon, Jr., Sami A. Khalil, and David H. Lewis,† Philadelphia, Pa.*

A diminution in the intensity of the first heart sound in acute myocardial infarction has been noted in man. To explore this further, 2 new technics were applied in the experimental animal, namely, intracardiac phonocardiography and direct coronary artery embolization.

In intact, anesthetized dogs, the anterior descending or the circumflex branch of the left coronary artery was catheterized through one of the carotid arteries, using the West coronary artery catheter. Measurements were made of left ventricular and chest sounds, left atrial, left ventricular, and aortic pressures, and electrocardiogram. Repeated coronary embolization was done using 0.2-0.6 ml. doses of a 1 per cent lycopodium spore suspension.

In the control intracardiac phonocardiogram, the first heart sound showed 2 major vibrations associated with mitral closure and aortic opening, respectively. Initial embolization resulted in a transient decrease in the intensity of the later component. Changes in the second sound were inconstant. With this, there was slight to moderate hypotension, slight increase in left atrial pressure, and the electrocardiographic evidences of acute injury. Subsequent embolizations resulted in a progressive decrease in the intensity of both components of the first heart sound with a decrease in the intensity of the second heart sound. In addition, there appeared a loud presystolic gallop. This stage was associated with progressive hypotension, increasing left atrial pressure and the electrocardiographic evidences of acute infarction. The changes in the chest sounds paralleled those within the heart. The decrease in the intensity of the first heart sound bore no constant relationship to the pressure level, heart rate, or the duration of isometric contraction.

Sympathomimetic Amines in Complete A-V Heart Block During Experimental Acidosis and Hyperkalemia

Santiago V. Guzman, Antonio C. de Leon, Jr., James W. West, and Samuel Bellet, Philadelphia, Pa.*

Isoproterenol, epinephrine and similar drugs have been effectively used in the treatment of Stokes-Adams attacks. However, failure in reactivating ventricular beating has been encountered with these drugs, whereas molar sodium lactate has proved to be effective. This raises the question of the possible influence of pH and electrolyte changes on the response of the ventricular pacemaker to the sympathomimetic amines.

The effect of intravenous and intracoronary arterial injections of isoproterenol (0.1-1 μg. per Kg.), epinephrine (0.5-2 μg. per Kg.) and norepinephrine (0.5-2 μg. per Kg.) on the idioventricular rate was studied in 16 chronic dogs with complete A-V heart block under conditions of acidosis and/or hyperkalemia. Ammonium chloride acidosis caused a decrease in pH (from 7.4 to 6.9), and plasma Na, as well as a marked increase in plasma K (from 4-9 mEq. per L.). This was accompanied by a marked decrease in idioventricular rate (from 46 to 22 beats per minute). Respiratory acidosis induced by inhalation of 20 per cent CO_2 resulted in a greater decrease in pH (from 7.4 to 6.7), and no significant change in plasma K or Na levels but a moderate decrease in idioventricular rate (from 50 to 40 beats per minute). In both types of acidosis, the 3 sympathomimetic amines showed a decreasing effectiveness in accelerating the idioventricular rate which paralleled the progressive drop in pH. Furthermore, refractoriness to these drugs was noted at pH levels below 7.0. Hyperkalemia produced by infusion of isotonic KCl resulted in a marked increase in plasma K (4 to 11 mEq. per L.) and a decrease in Na, along with

a slight drop in pH (7.3 to 7.2) and a marked decrease in idioventricular rate. However, the effect of the sympathomimetic amines on the idioventricular rate was unaltered.

These studies suggest that the refractoriness of the sympathomimetic amines is due to the lowered pH level since correction of the pH restores their effectiveness. The marked slowing of the idioventricular rate in the presence of acidosis and hyperkalemia suggests their possible role in the precipitation and maintenance of Stokes-Adams attacks.

Effect of Histamine upon Large and Small Vessels of the Dog Forelimb

Francis J. Haddy, Chicago, Ill.

Histamine was injected or infused into the brachial arteries of 75 dogs. The rate of blood flow in the brachial artery was measured or held constant. Pressures were measured in the brachial artery, a foot pad small artery (0.5 mm.), a subcutaneous small vein (0.5 mm.), a muscle small vein (0.5 mm.) and in the cephalic vein. Instantaneous injection of 0.1 to 5.0 γ histamine base increased flow rate with foreleg skin intact or removed, greatly decreased pressures in small arteries, moderately increased pressures in muscle small veins and slightly increased pressures in subcutaneous small veins. With the rate of blood flow held constant, brachial and small arterial pressures decreased and venous pressures did not change. Infusion of 1 to 20 γ histamine base per minute progressively but equally decreased brachial and small arterial pressures without affecting venous pressures. Infusion rates greater than 20 γ per minute elevated muscle and subcutaneous small vein pressures to levels as high as 50 mm. Hg. This finding occurred even after splitting the skin and fascia from knee to ankle. Subcutaneous and muscular edema became visually apparent whenever small venous pressures remained well elevated for 10 minutes. These findings indicate that histamine is an arteriolar dilator in low concentrations but also a constrictor of large veins in high concentrations. Therefore, histamine hypotension may result both from a decrease in peripheral resistance and from a decrease in venous return (peripheral pooling subsequent to arteriolar dilatation and large venous constriction) and histamine edema from elevation of capillary hydrostatic pressure (subsequent to arteriolar dilatation and venous constriction) rather than from increase in capillary permeability.

Coronary Arteriography: I. Controlled Experimental Method; II. Modifications of Coronary Circulation

Cameron Haight, Melvin M. Figley, Herbert Sloan, Waverly J. Ellsworth, John A. Meyer, Marvin S. Berk, and Delbert E. Boblitt, Ann Arbor, Mich.

Anticipating the use of coronary arteriography for the detection of asymptomatic coronary artery disease, or for the preoperative evaluation of symptomatic patients, an endeavor has been made to learn from experiments on dogs the optimum type and concentration of contrast agent and the volume and speed of injection for adequate arterial visualization. Results to date indicate that .25 cc. of 70 per cent Hypaque per pound, delivered in 3 heart beats by a catheter with several side holes and with its tip in the base of the aorta, regularly provides satisfactory opacification with negligible alterations in cardiac function.

Efforts have also been made to improve coronary opacification by controlling the cardiac output and by administering vasodilating drugs. Reduction of cardiac output by inferior vena caval occlusion, by increased intrathoracic pressure, and by balloon occlusion of the ascending aorta causes the coronary arteries to widen slightly. Vasodilators, such as amyl nitrite, nitroglycerin, and Mecholyl, cause them to widen up to 50 per cent above their size prior to the use of these drugs, even though there may be no alteration of pulse or blood pressure. Presumably the coronary flow is correspondingly increased.

Physiologic phenomena concerning ventricular ejection and coronary flow are readily appreciated by coronary arteriography; this method may also prove of value for pharmacologic investigations upon the coronary arteries.

The effect of variations in the cardiac output and the use of vasodilating drugs have also been studied in animals with experimentally produced partial occlusion of a branch of the left coronary artery.

Coronary-Internal Mammary Artery Anastomoses

Robert J. Hall, Donald E. Gregg, and Edward M. Khouri, Washington, D. C.

For chronic coronary circulation studies, anastomosis of a systemic artery to the circumflex coronary artery was attempted by suture and nonsuture technics in large dogs. During suture anastomosis of the coronary to the carotid or internal mammary artery, coronary flow was maintained by an indwelling plastic tube connected to the aorta or to a perfusion bottle of arterial blood. Thrombotic occlusion occurred in majority of these dogs. With a nonsuture technic the cut end of the internal mammary artery was everted over a "tooled" Nylon or stainless steel cuff. The everted vessel was secured over the cuff by 2 circumferential ligatures and the cuffed end was inserted into

an inverted T" incision in the previously dissected, p imally tied circumflex artery. Two additional li ures about the circumflex fixed the cuff in place a circulation was restored, generally in less than 1 seconds. Technical problems in inserting the e d internal mammary artery within the circumfl resulted in fatality in 6 dogs at or within 36 h s of surgery. Of the remaining 25 surviving d . 3 subsequently died, demonstrating thromb s at the anastomosis 2, 3, and 13 days postop tively. Twenty-two dogs survive chronically wi normal electrocardiograms. Where tested, p nt anastomoses have been demonstrated by co rast aortography. The high yield of patent an tomoses confirms the findings of Carter and R . These dogs are being followed chronically to etermine the duration of patency of the anastos sis and to study the normal coronary flow during rest and exercise.

Renal Excretion of Sodium in Arterial Hypertension

Irwin B. Hanenson, Hertha H. Taussky, Nathan Polisky, William Ransohoff, and Benjamin F. Miller, Cincinnati, Ohio

In 16 patients with essential hypertension we have confirmed the observations of others that such individuals exerete sodium more rapidly following a hypertonic saline infusion than do normotensives. Two subjects with labile blood pressure showed a normal exeretion pattern.

Four patients with secondary hypertension were similarly studied. In 2 with Cushing's syndrome and 1 with pheochromocytoma, the abnormal sodium response was observed. In a boy aged 11, with coaretation of the aorta, sodium exeretion was normal.

To investigate the possibility that cerebral sodium receptors similar to osmoreceptors could be responsible for the hypertensive sodium exeretion pattern, hypertonic saline was infused into the carotid artery of 4 essential hypertensives and 1 control subject. The amount was designed to increase the cerebral serum sodium concentration without changing that of the rest of the body. This produced no change in sodium exeretion. However, urine flow decreased, indicating osmoreceptor stimulation.

In a subject with moderately severe hypertension, the effect on sodium exeretion of hypertonic saline could not be produced by expansion of blood volume with iso-oncotic albumin nor by the infusion of an equivalent amount of salt as isotonic saline.

Restriction of dietary sodium intake to less than 1 m. per day altered the sodium exeretion pattern toward towards normal in both patients with Cushing's syndrome, and 2 essential hypertensives. Contrariwise, 30 Gm. of salt per day to a normal subject showed an increase in the exeretion test to borderline hypertensive levels. No change in renal function was observed with either diet.

Cardiac Malformations in the Rat Produced by Exposure of the Mother to 6 Per Cent Carbon Dioxide During Pregnancy

Olga M. Haring, Chicago, Ill.

The purpose of this study was to observe the effect of increased carbon dioxide tensions on fetal growth when applied at different times of embryonic development.

Fifty-five pregnant rats were exposed in groups of 2 for 24 hours to 6 per cent carbon dioxide with 20 per cent oxygen and 74 per cent nitrogen at different stages during gestation. The earliest exposure was on the seventh day of gestation, the latest on the twenty-first day. After delivery at term the newborn rats were immediately weighed, measured, observed for visible malformations and then fixed in formalin. The total number of offspring from the 55 treated rats was 246. One hundred hearts out of the 246 were serially sectioned and studied histologically. The findings were compared with 25 control hearts obtained from untreated rat offspring. The observations presented in these 100 hearts are the result of exposure on the seventh, eighth, ninth and tenth days of gestation. Some of the significant cardiac findings are the following:

1. Large and patent ductus arteriosus in 90 per cent, functional closure of the ductus in 10 per cent. (In the control group there was a functional closure of the ductus in 85 per cent.)

2. Thickening of the endocardium, particularly in the atria.

3. Myocardial hypertrophy.

Long-Term Studies of Blood Pressure: Prognostic Reliability of the Cold Pressor Test and Observations on Blood Pressure Variation

William R. Harlan, Durham, N. C.

Long-term studies of blood pressure afford the only reliable means of evaluating the predictive value of the cold pressor test and of describing the changes in blood pressure related to weight and aging.

The vascular response to the cold pressor test was measured in 201 healthy young men (mean age 23.6 years) selected for naval flight training in 1940. The test was performed as described by Hines and Brown. This group was re-examined at 12- and 18-year intervals. Using the modified criteria suggested by Windeshiem, Roth, and

Hines 82 (40.8 per cent) of the group were classed as "normal reactors," 106 (52.7 per cent) as hyperreactors, and a group of 13 (6.3 per cent) had basal diastolic levels greater than 90 mm. Hg. At the 18-year follow-up, definite hypertension (with diastolic pressure of 100 mm. Hg or greater) was present in 5 of the hyperreactor group (4.7 per cent of this subgroup), 1 of the "normal reactor" group (1.2 per cent), and 3 (23.1 per cent) of the group with elevated baseline pressures. Fourteen subjects (8 hyperreactors, 4 normal reactors, and 2 with elevated basal levels) had diastolic blood pressures between 90 and 100 mm. Hg. The cold pressor test was repeated in 40 of the subjects with poor agreement between the initial results and those obtained 18 years later. Marked individual variability of response was noted and there appeared to be no definite changes in reactivity associated with age. There was no correlation between the results of the cold pressor test and the development of hypertension or other cardiovascular disease.

Follow-up study of this group and a similar group of 300 permit correlations of blood pressure with age, weight, and physical condition.

The cold pressor response has been accepted extensively as a test of vascular reactivity, and the theory offered that a state of vascular hyperreactivity forms a prelude to permanently elevated blood pressure. The results of the present study indicate that the test had little value in predicting the development of hypertension in this selected group.

Electromagnetic Plethysmography, a New Technic for Estimating Instantaneous Changes in Left Ventricular Volume in Awake, Intact Animals

Edward W. Hawthorne, Sheridan L. C. Perry, and Mary Gaspar, Washington, D. C.

Approximations of the instantaneous changes in left ventricular volume have been determined in intact dogs using a new method of electromagnetic plethysmography. Volume curves have been, additionally, obtained in open chest dogs. The curves obtained are reminiscent of classical recordings of ventricular volume by oncometric methods. Details of the method appear in a preliminary report. A 2½ turn helix of very fine mercury filled rubber tubing was wrapped around and sutured to the ventricular epicardium so as not to include the right ventricle. Insulated flexible wire leads from the helix were brought together longitudinal to the heart, tightly twisted and exteriorized. These leads were then connected to a null detector whose output passes through a rectifier and inverter and thence to a DC Sanborn Recording System. A large external coil of wire was connected to an audio-frequency power oscillator. This coil, when energized, produces an oscillating electromagnetic field within the dog, properly oriented. This field is inductively coupled to the internal ventricular helix which produces an EMF proportional to changes in instantaneous left ventricular volume. Recordings have been made in both awake and anesthetized dogs and the effects of epinephrine, rapid fluid infusion, eating and loud noises have been observed. Preliminary studies indicate that the instantaneous changes in stroke volume as obtained by this method bear a linear relation to those secured by conventional means in acute open chest experiments.

Studies in Differential Vectorcardiography of the Dog: III. Effect of Posture on the Spatial QRS Loop in the Normal Dog

Herman K. Hellerstein, Cleveland, Ohio, and Robert L. Hamlin, Columbus, Ohio

The effect of change in posture (right lateral, left lateral, dorsal supine) on the isolated QRS spatial loop of 16 normal dogs was studied. Vectorcardiograms were obtained using the equilateral tetrahedral reference system.

When the animals were moved from the right to left lateral posture the direction of the inscription did not change in the horizontal and sagittal planes but reversed in the frontal loop in five instances. The mean electrical axis shifted rightward in 7 dogs and leftward in 4. Vectors 1 (initial cephalic), 2 (caudal), and 3 (terminal cephalic) remained similarly oriented.

Greater changes occurred in the dorsal supine recumbency. The direction of inscription did not change in the horizontal and sagittal planes but in 9 cases reversed in the frontal plane. The electrical axis shifted rightward in 6, and leftward in 5. The sagittal QRS loop became narrower in 14 cases. The frontal QRS loop narrowed in 6 dogs and widened in 7. Vector 1 lost its cephalad orientation in 14 cases and became directed ventrally. Vector 3 lost its dorsal orientation in 13 cases. These changes suggest a significant rotation of the heart on the transverse axis with dorsal movement of the apex.

Spatial magnitude electrocardiograms and spatial velocity electrocardiograms remained unchanged in all 3 postures.

Summary: Changes in posture produced changes in the orientation of the isolated spatial QRS loop, but not in the basic spatial configuration, inscription composition of component major vectors or in the form of the spatial magnitude and velocity electrocardiograms.

Mode of Death in Coronary Artery Disease: Electrocardiographic and Clinical-Pathologic Correlation

Herman K. Hellerstein and David J. Turell, Cleveland, Ohio

The exact moment of conversion to the terminal rhythm was obtained in 59 of 84 patients with coronary artery disease on whom electrocardiograms had been taken during the terminal episode. The cases were classified as to cause and mode of death after correlation of electrocardiographic, clinical and autopsy data.

Eleven patients had coronary disease, but died of other causes. Of the remaining 73 patients, 61 died following an acute myocardial infarction, coronary thrombosis, or coronary insufficiency, 6 died of chronic congestive failure, and 6 of recurrent Stokes-Adams episodes.

Primary mechanism failure caused sudden death in 39.7 per cent (29/73) of those dying of coronary disease. In 13 cases of sudden death (less than 5 minutes) in which the exact moment of death was recorded, abrupt ventricular standstill occurred in 10 (77 per cent) and ventricular fibrillation in 3 (23.0 per cent). Sudden death occurred in 52.4 per cent (22/42) of men dying of coronary disease and in only 22.6 per cent (7/31) of the women.

Primary myocardial failure resulted in gradual death in 60.3 per cent (44/73). Irreversible shock occurred in 11 (25.0 per cent), severe congestive failure in 4 (9.1 per cent), and both shock and failure in 29 (65.9 per cent). The terminal episodes lasted from 15 minutes to 2 days. Of 37 patients in whom the moment of death was recorded, ventricular standstill occurred in 78.4 per cent (29/37), and ventricular fibrillation in 8 cases (21.6 per cent), 4 of which appeared postasystole. Approximately equal numbers of men and women died gradually, 20 and 24 respectively.

Paroxysmal Ventricular Tachycardia: A Ten-Year Study

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This analysis includes 83 episodes of PVT in 59 patients. There were 38 persistent and 45 intermittent episodes. Although the youngest patient was 9 months of age and the eldest 97 years, 80 per cent of the patients were between the fifth and seventh decades. There were 33 males and 26 females. Rate of the tachycardia varied from 104 to 231 and its duration from a few seconds to over 7 days. Electrocardiograms before and after the paroxysms were available in 38 of 57 patients, and in 30 per cent atrial fibrillation was recorded before and after the PVT. Two of the tracings showed bidirectional ventricular tachycardia. Coronary artery disease, with or without hypertension, was present in 42 cases (74 per cent), and 13 of these had acute myocardial infarction. Rheumatic heart disease occurred in 7 patients (12 per cent). Six patients (10 per cent) had no organic heart disease. Digitalis had been given to 32 patients (54 per cent) and in 16 of these there was digitalis intoxication. Congestive heart failure was precipitated or aggravated by the PVT in 60 per cent of the patients. Dyspnea and weakness were the most frequent symptoms, but there were often chest pain and palpitation, and occasionally cerebral manifestations.

In about 30 per cent of the persistent cases, the blood pressure had to be maintained with vasopressor agents, most often norepinephrine. The effectiveness of quinidine therapy was confirmed. However, many PVT episodes reverted upon administration of procaine amide, which appeared the most effective intravenous preparation. Simultaneous vasopressor agents were at times necessary because of a drop in the blood pressure, a definite hazard of procaine amide therapy. Potassium therapy was a valuable adjunct in the cases due to digitalis overdosage, but not as effective as in paroxysmal atrial tachycardia with block. Combinations of drugs were occasionally necessary in refractory cases. Chloroquine, Pacatal, and Atarax offer promise, and deserve more extensive trial. Although only 5 patients with persistent PVT died of the arrhythmia itself, the long-term prognosis was poor, as 31 of these patients (54 per cent) died within 10 months after the onset of ventricular tachycardia. The mortality rate was even higher (77 per cent) in the patients in whom PVT complicated acute myocardial infarction.

Clinical Use of Cardiac Pacemaker with Myocardial Electrode

Paul C. Hodges, Earl E. Bakken, and C. Walton Lillehei, Minneapolis, Minn.

The rapidly expanding use, during the past few years, of open technics for the repair of septal defects, has produced a small but important group of patients with transient or persistent atrioventricular dissociation. The development and use of the myocardial electrode with a cardiac pacemaker has completely altered the prognosis for those patients with surgically induced complete heart block. By this method, good ventricular function with adequate systemic blood pressure is easily maintained for days, if necessary, without patient discomfort. The technic was first utilized clinically January 30, 1957, and since that time more than 50 patients have been treated in this fashion by our group. The clinical information gained from this experience, together with experimental

data and improvements in equipment which have occurred, form the basis of this report.

The majority of patients with surgically induced dissociation convert to normal rhythm within a few days or weeks and thus need pacemaker stimulation for lesser periods of time. A more serious problem has been encountered in those patients with permanent dissociation who may require artificial stimulation for a period of weeks or months.

These problems have been investigated from the point of view of optimal stimulus (wave shape, amplitude, and duration), maintenance of the myocardial wire and the use of Isuprel and other adjuvants. The indications for discontinuance of stimulation and methods of weaning the chronically blocked patient from the pacemaker have also been studied.

A technic also has been developed for percutaneous insertion of myocardial electrodes in order to make available for nonsurgical patients with complete heart block the advantages of internal stimulation.

Hereditary Hemorrhagic Telangiectasia and Pulmonary Arteriovenous Fistula: Study of Six Generations of a Large Family

Corrin H. Hodgson, C. Allen Good, Howard B. Burchell, and O. Theron Clagett, Rochester, Minn.

A large family, many of whom had hereditary hemorrhagic telangiectasia, was surveyed to determine the number who had telangiectasia and the number who had pulmonary arteriovenous fistulas.

Information regarding the presence or absence of telangiectasia was obtained on more than 200 members of this family and approximately 40 per cent were found to have it. Details regarding the incidence of the condition in the sexes, the age groups, and the 6 generations are available in addition to general information on hereditary hemorrhagic telangiectasia.

Pulmonary arteriovenous fistulas were found to occur in approximately 5 per cent of the members of this family. One half of them were discovered by taking routine roentgenograms of the thorax of more than 120 people and the others were found by searching the family history. A brief report of each of the 13 known cases is available. Clinical, roentgenologic, physiologic and surgical aspects of pulmonary arteriovenous fistulas have been investigated.

Left Ventricular-Right Atrial Shunts

Herbert N. Hultgren, Frank Gerbode, John Osborn, San Francisco, Calif., and Denis Melrose, London, England

Successful surgical closure of a ventricular septal defect communicating with the right atrium through an abnormal leaflet of the tricuspid valve has been accomplished in 5 patients without mortality. Study of these patients before and after surgery has provided an opportunity to determine the clinical diagnostic features of the lesion. Correct diagnosis is important since an attempt at operative repair without employing extracorporeal circulation is dangerous and usually unsuccessful.

The patients studied were from 5 to 42 years of age. All except 1 had moderate to severe physical incapacity due to pulmonary congestion. A pansystolic murmur and palpable thrill along the lower sternal margin were present in every patient. Wide splitting of the second sound at the pulmonic area was not present. The electrocardiogram was not distinctive.

Roentgenograms usually indicated enlargement of the right atrium and right ventricle, as well as fullness of the pulmonary vessels. Cardiac catheterization studies revealed in each patient a left to right shunt at the atrial level with a resulting pulmonary blood flow varying from 1.8 to 3.5 times the peripheral blood flow. Pulmonary artery systolic pressures varied from 25 to 60 mm. Hg.

At surgery, systolic bulging of the right atrium was striking. Digital occlusion of the defect through the right atrium abolished the thrill and produced cardiac slowing and a rise in blood pressure. Successful surgical repair was accomplished through a right atriotomy incision during perfusion with a film-type oxygenator without stopping the heart. All patients are now asymptomatic and the physical signs of the shunt have disappeared.

Ultra-Low Frequency Force Ballistocardiogram in Rheumatic Heart Disease

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Fifty-eight subjects with known rheumatic heart disease have been studied with the ultra-low frequency acceleration (force) ballistocardiogram. The method is that of Rappaport (pendulum bed). Patients fell into the following categories: mitral insufficiency, mitral stenosis, combined mitral stenosis and insufficiency, aortic valve disease, combined mitral and aortic valve disease, and a miscellaneous group of nonspecific ballistocardiographic abnormalities.

Study of these groups reveals certain characteristic patterns. In mitral stenosis, the ULF-BCG reveals a large variable "H" wave, an abnormal low lying vibratory complex in the position normally occupied by the G, H and I waves (termed "GHI"), a low amplititude IJ complex, and small diastolic waves.

In mitral insufficiency, the systolic waves are small and the J may be widened and notched. The major abnormality consists of very tall L, M and N waves, often 2 to 3 times the amplitude of the IJ complex.

The aortic stenosis tracings are distinguished by a small H, deep widened I, and a low amplitude wide J with coarse notching, often double peaked, and " peak on the same plateau.

Aortic insufficiency presents very large systolic complexes, the largest amplitude of any ballistocardiographic tracing seen. The I is deep, J is of very large amplitude and the J" is represented by a deep negative wave.

These configurational abnormalities allow ready identification of the pure physiologic valvular defects. Combined lesions are recognizable and myocardial failure can be distinguished from valvular defects.

Frequency Characteristics of Extra-Sounds

Aldo Jacono, Chicago, Ill., and Charlotte Friedland, Mexico City, Mexico

The frequency characteristics of cardiac murmurs have been studied with different recording methods, including calibrated, filtered, and selective phonocardiography, but no systematic study was done in regard to the frequencies of the normal and pathologic sounds.

In normal patients, and in cases with different kinds of heart diseases, the third and fourth sound, the opening snap, and split second sound have now been investigated in normal subjects and in the cardiac patient by means of selective phonocardiography.

The third sound was studied in 47 cases; the fourth sound, in 23 cases; the opening snap, in 15 cases; and the splitting of the second sound, in 10 cases. Twenty-five subjects were normal, 4 had congestive heart failure, 6 had suffered from myocardial infarction, 16 had rheumatic fever, 13 had rheumatic heart disease, and 10 had various other types of heart diseases. The age of these cases ranged from 4 to 70 years.

The third sound appeared at a frequency of 20 c.p.s. and was well recorded up to 60 to 80 c.p.s. Only in 7 cases, recording was possible up to 120-160 c.p.s.

The fourth sound started at 20 c.p.s. in all cases; it could be recorded up to 60-80 in 12 cases; to 100-120 in 5 cases; to 140-160 in 4 cases; and to 180-200 in 3 cases. The opening snap appeared at a frequency of 40 c.p.s. and lasted till frequencies ranging from 150 to over 300 c.p.s. The second component of the second sound was in the range from 20-40 up to 300-400 c.p.s.

No significant frequency variation was found between normal subject and cardiac cases. No relationship was noted with the age of the patients. It was not possible to differentiate the second from the fourth heart sound by means of sound frequencies. The opening snap and the split second sound are in the same frequency range. It is usually possible to differentiate an opening snap and a split second sound from the "gallop sounds" by means of selective phonocardiography.

Naturally Occurring Arterial Anastomoses in the Human Heart

Thomas N. James and George E. Burch, New Orleans, La.

Despite current interest in improving blood supply to the human myocardium, the state of naturally occurring arterial anastomoses remains a confused subject. There are such widely differing opinions as (1) consideration of the coronary arteries as end-arteries, and (2) belief in the general presence of large functioning collateral arteries at all age groups.

All methods for studying the collateral arteries in the heart have certain disadvantages, most of which err on the side of not demonstrating anastomoses which actually exist.

In a group of 81 human hearts studied by vinylite injection and hydrochloric acid corrosion, the characteristics and extent of arterial anastomoses were observed. Many of the normal hearts in this study, including both young and old patients, had grossly demonstrable arterial anastomoses. Most of these were larger than 40 μ in diameter. There was entirely different anastomoses present in hearts from patients with chronic occlusive coronary artery disease. The anastomoses in the normal hearts were usually thinner and straight or gently curving, whereas those in the diseased hearts were tortuous and elongated.

If many (and possibly all) normal hearts possess grossly demonstrable arterial anastomoses, the rationale of subjecting the diseased heart to various procedures in the hope of inducing revascularization of the myocardium becomes questionable. A more rewarding approach may be to determine what factors govern the function of normally occurring arterial anastomoses.

Cardiac-in-Agriculture Demonstration

Lewis E. January, Joseph P. Stoikovic, Iowa City, Iowa, Thomas A. Robb, Washington, Iowa, and Warren L. Van Eschen, Cedar Rapids, Iowa.

A 2-year demonstration was undertaken to explore the feasibility of applying to the cardiac and occupational problems of agricultural workers the principles and technics of the work evaluation units for industrial workers.

Forty-six patients, 3 of them women, participated in the demonstration. They received a thorough examination by a cardiologist who established a diagnosis and assigned a functional and therapeutic classification. They were interviewed on their farms by a vocational counsellor and by the County Extension Director. Recommendations based on these interviews were presented to the patient at a conference attended by the patient's referring physician. The following types of cardiac disabilities were represented in the study: proven myocardial infarction in 12 cases, rheumatic heart disease and atherosclerotic heart disease in 9 each, angina pectoris in 4, heart disease due to thoracic deformity in 1, congenital heart disease, hypertensive heart disease and neurocirculatory asthenia in 2 each. Five had no heart disease.

Over a 2-year period, the demonstration produced the following results:

Surgical treatment for mitral stenosis	1
Continue farming without change	11
Continue farming but avoid strenuous labor	10
Continue farming temporarily for a year or two	3
Continue farming by use of partnership or lease arrangements	7
Continue farming by specific changes	2
Discontinue farming and seek a more sedentary occupation	5
Discontinue farming and retire	5
Restrict activity to housework	2

The organization and technics of the program have proven workable and the program has been acceptable to physicians and patients alike. The number of patients in the study is small. We believe, however, that we have demonstrated that it is medically safe and economically sound to deal with the problem of the cardiac farmer in the manner described here.

The cardiac status did not deteriorate in any patient as a result of the suggested change of work habits or farm management. Some patients improved. In addition, all patients benefited from the vocational and farm counseling.

Postoperative Pericarditis in Patients Undergoing Cardiac Surgery

John L. Johnson, Pasadena, Calif.

Postoperative pericarditis and pleuroeffusion has been observed in 10 cases of congenital heart disease undergoing various operations requiring opening of the pericardium and appears between 1 and 2 weeks postoperatively. The age group varies between 2 and 26 years with the majority being in the pediatric age group. Seven of the cases followed atrial septal closure, 2 followed ventricular approach for correction of pulmonary stenosis, and 1 supracardiac approach to congenital aortic stenosis.

The first symptom is elevation of temperature followed by pains over the left chest and frequently in the right. The pain in the older individual radiates over the left shoulder and into the arm. Dyspnea occurred in most cases requiring oxygen for relief. Coughing and a friction rub was noted in at least 50 per cent of the cases. Chest films demonstrated a sudden increase in the size of the cardiac shadow, which on fluoroscopy sometimes showed evidence of fluid. In 2 or 3 days following the onset of the pericardial effusion, a pleuroeffusion was noted which usually disappeared in a week. Liver enlargement and tenderness occurred in 4 of the patients associated with increased venous distention of the neck. Characteristic electrocardiographic signs of pericardial effusion were observed. Blood cultures were repeatedly negative. Pericardial taps were performed on only 2 of the patients with findings of bloody fluid but no signs of infection. Treatment consisted of digitalization, sodium restriction, bed rest, and oxygen as needed. Antibiotics were given to about half the cases with no particular effect. The acute phase of the syndrome usually lasts approximately 1 week, after which the chest pain and discomfort disappear. Once cleared, there have been no recurrences.

Reversal of Cardiovascular Shunts Following the Valsalva Maneuver

Anthony D. Jose and William R. Milnor, Baltimore, Md.

Patients with congenital cardiovascular defects and predominantly left-to-right shunts sometimes exhibit temporary reversal of the shunt, with a resulting drop in arterial oxygen saturation. To investigate the physiologic and diagnostic implications of this phenomenon, we have measured the effect of a 10-second Valsalva maneuver on arterial oxygen saturation (measured continuously by withdrawing blood through a cuvette densitometer) in 17 patients with congenital or acquired heart disease.

Reduced venous inflow during the Valsalva maneuver is followed on release by suddenly increased inflow, elevating pressures first in the right heart and some seconds later in the left heart. This asynchronous pressure rise may produce right-to-left flow through cardiac defects.

Six control subjects with valvular lesions, cor pulmonale, or normal hearts showed no measurable fall in arterial saturation following release. Five cases of atrial septal defect uncomplicated by pulmonary hypertension showed a sharp desaturation equivalent to 1 to 6 per cent of arterial

oxygen capacity, appearing 3 to 5 seconds after release. Six cases of congenital atrial or ventricular septal defect or patent ductus, with right ventricular systolic pressures of 80 mm. mercury or more, showed desaturation of 7 to 20 per cent. Two cases with moderate pulmonary hypertension without septal defects showed no desaturation after release, but a rise of 5 to 10 per cent occurred during the maneuver.

Results suggest that the degree of unsaturation following the maneuver is proportional to the resistance to normal flow beyond the defect, and may therefore be increased by high pulmonary vascular resistance, pulmonic stenosis, or tricuspid obstruction.

Group A Streptococcal Cardiac Lesions in Rabbits

Robert E. Kalina, Philip L. Eckman, and Joel G. Brunson, Minneapolis, Minn.

Grouped hybrid albino rabbits were given an intravenous (1 ml.) or a pharyngeal (0.5 ml.) injection of a group A streptococcal culture at varied intervals in conjunction with rotation in a modified Noble-Collip drum.

Only one of 24 animals given pharyngeal streptococci died within 24 hours. In contrast, 4 of 7 animals given intravenous streptococci 1 week prior to rotation, and 5 of 8 given intravenous streptococci simultaneously with rotation, died acutely.

In 54 of the 60 animals extensive cardiac changes were observed. These were both "bland" and "septic" in character. The bland lesions consisted of areas of focal to diffuse myocardial necrosis and cellular reaction, and edema and hypercellularity of the valves. The cellular reaction was composed of Anitschkow, mononuclear, and giant cells. In addition, hyaline fibrinoid material was present in the coronary arterial walls, perivascular spaces, and substance of the valves. Streptococci were observed occasionally in the arterial and valvular lesions, but the changes generally resembled those of acute rheumatic carditis. The septic lesions were similar, but clumps of microorganisms were present, and there were numerous heterophilic cells in addition to those described above. In some instances, frank bacterial vegetations were present on the valve surfaces.

In an effort to gain further information concerning the pathogenesis of the lesions, 25 additional rabbits were given group A streptococci in conjunction with the administration of metaraminal bitartrate. Cardiac lesions strikingly similar to those described above occurred in 23 of these animals, suggesting that adrenal hormones may play an important role in the development of streptococcal cardiac lesions.

Evaluation of the Serum Glutamic Oxalacetic Transaminase Activity in Pericarditis

Robert B. Kalmansohn and Richard W. Kalmansohn, Los Angeles, Calif.

In the experimental animal with pericarditis, elevation of serum glutamic oxalacetic transaminase activity (SGO-T) is proportional to the severity of the subepicardial myocarditis. The clinical counterpart of the experimental animal has not been heretofore documented in the medical literature. We recently have studied the serial SGO-T titers in 7 patients with pericarditis: 5 had acute nonspecific pericarditis, and 2 had pericarditis associated with myocardial infarction. Six of the patients had elevated SGO-T titers; in 2 cases of nonspecific pericarditis, the peak levels were 116 and 165 units respectively. Four of the 6 patients with elevated SGO-T levels had peak ranges between 52 and 75 units. There was no apparent correlation in this series between the severity of the clinical picture and the degree of elevation of the SGO-T titer. It appears from these cases that the SGO-T activity is commonly elevated in pericarditis, and that the peak levels may be in the range seen in patients with acute myocardial infarction. Therefore, the SGO-T titer would not appear to be an accurate method of differentiating acute pericarditis from acute myocardial infarction unless the level was normal or very high (over 200 units); a normal level is consistent with pericarditis but rarely or never seen in myocardial infarction, while a level of over 200 units (commonly seen in cases of myocardial infarction) has not been recorded in cases of pericarditis.

Metabolic Fate of Potassium Used in Cardioplegia

Abraham Kaplan and Bernard Fisher, Pittsburgh, Pa.

There is a complete absence in the literature of experimental work regarding the metabolism and fate of potassium used as a cardioplegic agent. This paper is concerned with the metabolism of potassium citrate tagged with K^{42} used to produce cardiac arrest.

Dogs at random were divided into the following groups: (1) normothermic, (2) hypothermic, (3) hypothermia and digitalis, (4) hypothermia and coronary perfusion.

Following thoracotomy, venous inflow occlusion and clamping of the aorta, cardiac arrest was produced by injecting potassium citrate, 25 per cent, 2 ml., normal saline, 18 ml., and heparin, the solution containing K^{42}. At the onset of cardioplegia, blood samples from the coronary sinus and a piece of myocardium for assay were obtained. When venous inflow was re-established, the curve of dis-

appearance of radioactive K^+ in the myocardium was measured by means of a scintillation counter. Activity in samples of myocardium and the disappearance in the peripheral blood were measured.

Data, to date, on 30 animals has demonstrated that the phenomena which develop after the use of potassium do not fit in any given pattern, and they do not correlate with the amount of potassium used, time taken to reach a plateau, or number of counts of that plaeau. Results will be discussed more thoroughly on each group, but it may be postulated that the results are individualized and related to a trigger mechanism set off by K^+ at the cell level, but not necessarily due to K^+ itself.

Clinical Picture of Combined Aortic and Mitral Stenosis

Gordon Katznelson, Robert Jreissaty, Gilbert E. Levinson, Walter H. Abelmann,† and Laurence B. Ellis, Boston, Mass.

Nineteen of 127 patients studied by left heart catheterization were suspected clinically of having significant combined aortic and mitral stenosis. The following analysis deals with the 16 cases proven by catheterization. Thirteen were confirmed at surgery. Eleven had tight aortic stenosis with moderate (5) to severe (6) mitral stenosis. No unsuspected cases of the combined lesions were discovered. Mitral regurgitation, found in only 4, was never severe. None had significant aortic regurgitation.

In general, signs and symptoms of aortic and mitral stenosis were additive. All patients had moderate to severe symptoms. Almost all had aortic systolic and mitral diastolic murmurs, basal thrill, absent A_2, left atrial and biventricular enlargement radiologically, and p-mitrale (4 of 5 with sinus rhythm) and left ventricular hypertrophy electrocardiographically. An apical systolic murmur was always present, and its significance will be discussed. Two departures, however, appeared from the usual signs of mitral stenosis: opening snap was found in only 5 of 16 (by auscultation and phonocardiogram), and accentuated M_1 in only 3 of 11 with severe aortic stenosis. None of the signs of aortic stenosis was modified by the combination.

The natural history was dominated by features of mitral stenosis: women predominated (12), mean duration of symptoms was 7 years, 11 were in atrial fibrillation, and 4 suffered peripheral emboli.

The clinical diagnosis of coexistent aortic and mitral stenosis, based on the conventional signs of the separate lesions, is usually reliable. In the presence of aortic stenosis, certain features of the natural history suggest mitral stenosis, even when the physical findings are not fully characteristic.

Open Heart Surgery Using the Kay-Anderson Heart Lung Machine

Jerome H. Kay, Robert M. Anderson, and John Meihaus, Los Angeles, Calif.

During the past 4 years, the authors have developed an improved heart lung machine. This apparatus uses roller pumps and stationary stainless steel screens for oxygenation. In order to start a film, an automatic filmer has been developed. The entire oxygenator is sterilized by autoclaving. Using this apparatus, the authors have operated upon 3 patients with tetralogy of Fallot, 1 patient with valvular pulmonic stenosis and interatrial septal defect, and 14 patients with interventricular septal defects. There have been 2 deaths in this series, 1 due to cardiac tamponade, due to closure of the pericardial sac, which is no longer done. The second death occurred 2 hours following surgery. There is no chance of air or antifoam emboli since this apparatus does not use the bubbling principle and no bubbles are formed during the oxygenation. The apparatus is run by 1 person. It is easily assembled and cleaned. During the open heart procedure the authors allowed the temperature to drop in the patient to 31-33 degrees centigrade as measured by an esophageal lead. Very little anesthesia is required. In fact, the patients only receive a small amount of anectine during the period of bypass. A normal cardiac output is maintained during the period of bypass and patients have been done varying from 27 lbs. to 150 lbs. with this apparatus.

Recurrent Pulmonary Infarction in Healthy Young Men

Kaye H. Kilburn and Herbert O. Sieker, Durham, N. C.

The frequent occurrence of venous thrombosis and pulmonary embolization in elderly, immobilized, or cardiac patients is well known. Recurrent thrombophlebitis and pulmonary embolization in young healthy individuals has been less well recognized. In the past 5 years, 40 men under age 40 have been observed with pulmonary infarction. In 24 patients (15 of whom were under 30 years) pulmonary embolization could not be explained by antecedent heart disease, immobilization, or recent leg injury. Twenty-two of the 24 were white patients. Three had a familial history of the disease.

Lower extremity thrombophlebitis preceded pleuritic chest pain and hemoptysis in 17, and followed it in 2. Five had no history suggesting thrombophlebitis. Thrombophlebitis was recurrent in 16 and migrating in 3. Six patients had varicose leg veins; 5 had a vague past history of leg injury.

Multiple pulmonary infarctions were recognized in 1 patients, occurring several hours to 10 years apa . Thrombophlebitis without pulmonary symptom often occurred between such episodes. Five pati ts had 3 or more pulmonary infarcts and 2 pat ts died. Laboratory evidence of chronic pul nary hypertension was present in 5.

E stic stockings and anticoagulation with hepari and/or Dicumarol were the usual therapy. Out atient anticoagulation was difficult to maintain r was unsuccessful. Inferior vena cava ligation was done on 3 patients who had multiple infarc ons and there were no recurrences.

T is experience indicates that venous disease and pul onary embolization can occur in healthy, active young individuals. It may result in cor pulmon le or death. Interruption of the vena cava and the path of emboli should be seriously considered in recurrent embolization.

Effect of Continuous Positive and Negative Pressure Breathing on Intrathoracic Hemodynamics in Man

Kaye H. Kilburn and Herbert O. Sieker, Durham, N. C.

Knowledge of the circulatory effects of continuous positive or negative pressure breathing has been derived primarily from anesthetized animal studies. In normal man, continuously altered intrathoracic pressure has been shown to affect the peripheral circulation and renal function. This study was designed to elucidate the intrathoracic circulatory effects of continuous positive (PPB) and negative (NPB) pressure breathing in man.

Cardiac output, central blood volume, and plasma volume were measured in 34 normal subjects at rest and after equilibration on continuous positive or negative pressure breathing. Heart and respiratory rates, arterial and central venous pressures and airway pressures were monitored.

NPB from 12-22 cm. of H_2O raised the cardiac index 1.1 L. per minute per $M.^2$ (mean difference) and stroke volume 19 ml. (m.d.). Central blood volume did not change as calculated from dye curves or derived from number of scintillation counts over a field 5 cm. in diameter and 3.5 cm. inside the right posterior midchest.

PPB at 20-28 cm. of H_2O produced a fall in cardiac output of 1.3 L. per minute per $M.^2$ (m.d.) and central blood volume of 480 ml. (m.d.) if minute ventilation was unchanged. Count density of the peripheral lung field showed a decrease of 10 ± 5.5 per cent (m.d.). Cardiac output was unaltered in subjects hyperventilated on continuous PPB. Plasma volume remained unchanged with NPB and PPB.

The results suggest that continuous negative pressure breathing increases blood volume in the cardiac portion of the central reservoir without an increase in the lung periphery. During positive pressure breathing, exaggerated respiratory variations in intrathoracic pressure can compensate for decreased central blood volume and cardiac output.

Cardiopulmonary Dysfunction in Muscular Dystrophy

Kaye H. Kilburn, Herbert O. Sieker, and Albert Heyman, and John Eagan, Durham, N. C.

Congestive heart failure is a frequent cause of death in patients with muscular dystrophy, but there are few studies of cardiopulmonary function in this disorder. Lung volumes, ventilation, blood gases, ventilatory response to CO_2 and O_2 and, where indicated, cardiac output and pulmonary artery pressures were measured in 6 patients with myotonic and in 5 with facioscapulohumeral muscular dystrophy.

The maximal breathing capacity ranged from 49-82 per cent (47-99 L. per minute) of predicted value. The residual volume to total lung volume was above 20 per cent and the vital capacity was below 90 per cent (2.7-3.5 L.) of the predicted value in 6 patients. The pCO_2 was above 45 mm. Hg in 7 patients, and increased by oxygen breathing in 4.

Two patients were cyanotic but denied any cardiopulmonary symptoms. They showed oxygen saturations of 85 and 89 per cent, pCO_2 of 58.7 and 53.8 mm. Hg respectively and a decrease in all components of lung volumes. There was a normal ventilatory response to inhalation of 5 per cent CO_2. One patient had paroxysmal atrial fibrillation and the other showed paroxysmal right bundle-branch block.

Cardiac catheterization revealed elevated pulmonary wedge (20 mm. Hg) and artery pressures (27 mm. Hg) with a normal cardiac output (4.6 L. per minute). Oxygen breathing increased arterial oxygen saturation, raised pCO_2 and lowered pulmonary artery pressure. In 1 patient, weight reduction to below his normal level was coincident with improved arterial oxygen saturation and reversal of hypercapnia.

Diminution of lung volume and impairment of ventilation occur with muscular deterioration. The associated insidious development of the syndrome of alveolar hypoventilation probably contributes to congestive heart failure in patients with muscular dystrophy.

Separation of Left Ventricular Failure from Mitral Stenosis with Isoproterenol

Kaye H. Kilburn and Herbert O. Sieker, Durham, N. C.

The extent to which elevations of pulmonary artery pressure in mitral stenosis are due to left ven-

tricular failure has been difficult to detect during cardiac catheterization. Exercise response provides no differential because it produces a further rise in pulmonary artery pressure in both conditions. The effect of isoproterenol, which increases cardiac output without increasing oxygen demand, was measured in 8 patients with mitral stenosis. They were compared with 8 patients with congestive heart failure without valvular lesions and 7 normal subjects.

Pulmonary wedge, pulmonary artery and right ventricular pressures and cardiac outputs were measured during 10-15 minutes of 1-3 μg. per minute isoproterenol infusion into the pulmonary artery after baseline determinations.

In patients with mitral stenosis, isoproterenol infusion increased cardiac output 0.5 L. per minute per $M.^2$ mean difference (m.d.) and raised pulmonary artery pressure 4.1 mm. Hg (m.d.). In contrast, in congestive heart failure cardiac output increased 1.1 L. per minute per $M.^2$ (m.d.) but pulmonary artery pressure fell 6.0 mm. Hg (m.d.). In all cases of mitral stenosis, pulmonary artery pressure rose, while in congestive heart failure a pulmonary artery pressure always fell. In mitral stenosis, stroke volume was unchanged, while in heart failure it rose (25 ml. m.d.). In normal subjects, cardiac output rose 1.6 L./minute/$M.^2$ (m.d.) without altering pulmonary artery pressure.

Two patients with mitral stenosis without clinical evidence of heart failure were given isoproterenol infusions during cardiac catheterization. Cardiac output rose and pulmonary artery pressure fell. The presence of congestive heart failure was confirmed by subsequent response to diuretics.

Infusion of isoproterenol during cardiac catheterization appears useful in mitral stenosis to differentiate elevations of pulmonary artery pressure due to left ventricular failure.

Cardiac Lesions in Dogs Following Administration of Vasopressor Amines

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One hundred twenty-seven adult mongrel dogs were given a single intravenous injection of 1 of the following drugs in the dosage range indicated: methoxamine, mephentermine, phenylephrine, metaraminol (25 to 250 μg. per Kg.), epinephrine, and levarterenol (5 to 30 μg. per Kg.).

Forty-eight per cent of the animals showed gross and microscopic cardiac lesions. The incidence and severity of the lesions varied with the particular drug administered, but no correlation could be found between dose and incidence or severity of lesions.

The gross changes consisted of subendocardial and epicardial hemorrhages, areas of myocardial infarction, and extensive valvular edema and hemorrhage. Microscopic examination showed the presence of extensive muscle necrosis and inflammatory reaction, coronary arterial thrombi, and valvular edema, cellularity, and hemorrhage. In addition, hyaline fibrinoid material was present in the coronary arterial walls, perivascular spaces, and substance of the valves.

In addition to cardiac lesions, 41 per cent of the animals showed extensive areas of ischemic and hemorrhagic liver necrosis, and 35 per cent developed cortical necrosis of the kidneys. No lesions were observed in 27 control dogs.

These results suggest that administration of sympathomimetic amines to humans may be associated with the development of certain lesions, such as hepatic necrosis, and that they may enhance the development of cardiac lesions in patients with preexisting vascular disease.

Plasma Glyceride and Cholesterol Ester Fatty Acid Composition in Normal Individuals, and in Patients with Atherosclerosis and Lipoidoses

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A variety of blood lipids have been measured in patients with atherosclerosis and lipoidoses in an effort to clarify some aspects of fundamental lipid metabolism, to provide better understanding of the pathogenesis and chemical diagnosis of the disease process, and to make possible the evaluation of the effects of "therapeutic diets."

With improvements in methodology for chromatographic separation of plasma lipids, and qualitative and quantitative determination of fatty acids incorporated in these lipids (by alkaline isomerization and gas chromatography), data have accumulated which appear to be somewhat interpretable. Summarized, these data include the following:

1. Linoleic acid content of the plasma cholesterol esters in young normal individuals on an average diet approached 50 per cent of the total cholesterol ester fatty acids. This can be increased to a marked degree by inclusion of large amounts of linoleate in the diet.

2. Significant deviations from this pattern are found in some patients with atherosclerosis and lipoidoses, with particular reference to the amount of dietary linoleate required to achieve "normal" composition.

3. In early studies even greater deviations from the normal have been found in the fatty acid com-

position of the plasma glycerides in abnormal subjects. This was an unexpected finding.

In 1 patient with xanthomatous biliary cirrhosis maintained on very large amounts of linoleate, the plasma lipid pattern did not return to normal until major disappearance of xanthomatosis had been achieved. The possible relationship of this observation to the pattern in patients with atherosclerosis will be considered.

Acute Effects of Trimethidinium Methosulfate (WY-1395) on Blood Pressure, Cardiac Output, Renal Hemodynamics, and Pulse Rate in Man

Walter M. Kirkendall, Mark L. Armstrong, David C. Funk, and Ernest O. Theilen, Iowa City, Iowa

Trimethidinium methosulfate (d-N-dimethylamino-propyl-1-methyl-8, 8-dimethyl-3-azabicyclo [3:2:1] octane dimethosulfate) is a ganglionic blocking drug. Interest stems from its potency, long action, and the possibility that some of its hypotensive effect is of intracranial origin.

We studied 19 hypertensive patients over a 90-minute interval after intravenous injection of WY-1395 (1 to 3 mg.), by measuring cardiac output (CO) in 8 and glomerular filtration rate (C_I) and renal plasma flow (C_{PAH}) in 11. In most of these patients, and in 4 others, we measured blood pressure and pulse rate at frequent periods until 24 hours after the single injection.

We found little effect on CO or renal hemodynamics if supine blood pressure remained near normal (fell less than 10 per cent of mean) even though there was evidence of ganglionic blockade (orthostatic hypotension and blurring of vision). When supine blood pressure fell sharply, there were proportionate decreases in CO, C_I, and C_{PAH}. Total peripheral resistance increased in 6 studies, decreased in 6; renal vascular resistance increased in 14 instances, and fell in 13. If supine blood pressure fell, this usually occurred in 10 minutes, but was maximal in the second to fifth hour. Some patients still had orthostatic hypotension at the end of 24 hours. Pulse rate was unchanged. All patients who received 3 mg. of the drug developed hypotension in the supine position.

Most of the acute hemodynamic effects of WY-1395 are like those of other ganglionic blockers. However, the late prolonged depressor action is unusual and suggests the drug may have considerable clinical value.

Bilateral Internal Mammary Artery Ligation for Angina Pectoris After a Year: Clinical Results

J. Roderick Kitchell, and Thomas Barclay, Philadelphia, Pa.

Among the first 142 consecutive patients who had bilateral internal mammary artery ligation for angina pectoris a year or more ago, 12 could not be followed. There are 100 living: 30 are markedly improved, 27 moderately improved, and 20 slightly improved. Twenty-three were not helped.

There were 30 deaths, 5 occurring in the early stages of the study in patients who were operated upon while in an acute stage of myocardial infarction. Two others died during the original admission, one from lymphosarcoma discovered after mammary artery ligation had been done, and the other from pyelonephrosis, which was incipient at the time of surgery.

Of those who lived less than 6 months after leaving the hospital, 7 reported improvement in some degree but finally died of coronary disease. One who was improved died of pulmonary infarction following prostatectomy. Of those who lived more than 6 months after operation, 5 reported themselves improved; 4 of these died of coronary disease and 1 of a ruptured aortic aneurysm. Therefore, 13 of the 30 who died had some relief from their anginal distress after operation. Thus the percentage of improvement in the series of 130 cases is now 70 per cent.

It is emphasized that this operation should be done only for the relief of angina pectoris. It does not in any way alter the basic coronary disease present.

Effects of Tetraethylpyrophosphate (TEPP) on Transmembrane Potentials of an Atrial Pacemaker and Nonpacemaker Fibers of the Rabbit

Morris Kleinfeld, John Magin, and Edward Stein, New York, N. Y.

The atria of rabbits were placed in a lucite chamber and bathed by a slowly moving Ringers-Locke solution into which 95 per cent oxygen and 5 per cent CO_2 gases were continually bubbled. The temperature of the bath was maintained between 34 and 36 C. by a thermostatically controlled water jacket surrounding chamber. The transmembrane potentials of pacemaker and nonpacemaker fibers were obtained by the ultramicrode technic of intracellular recording.

When tetraethylpyrophosphate (TEPP) in concentrations of 5×10^{-7}M. was administered as a constant perfusion, the usual results were: (1) a slowing of atrial rate and subsequent block in conduction, with no significant change in membrane resting potential (MRP); (2) a reduction in slope of transmembrane potential of pacemaker fibers; (3) an accelerated repolarization and shortening of duration of the action potential of both types

of fibers; and (4) a variable degree of hyperpolarization of pacemaker fibers, particularly noticeable at slowed rates. During the latter period, there was also observed a decrease in the magnitude of the action potential in 4 out of 14 experiments. When the tissue was again exposed to original Ringers-Locke solution the above changes subsequently reverted to control record.

The modifying effects produced by TEPP resemble those of di-isopropyl fluorophosphate (DFP) on neural fibers reported by others. In contrast, hexaethyltetraphosphate (HETP) has been shown by Van Kloot to produce an irreversible block and a decrease in MRP in frog muscle.

The modifications observed with TEPP can be ascribed to its inactivation of cellular esterase and protein receptor. The failure of the membrane to depolarize can be more adequately explained by the alteration of receptor than in its inhibition of esterase. The acetylcholine cannot act normally on this changed receptor resulting in an impaired transmigration of sodium ions across membrane, and hence failure to depolarize it.

Metabolism and Coronary Flow of Electrically Active, Noncontracting Hearts

Robert M. Kohn, Buffalo, N. Y.

The membrane effects of impulse formation and conduction were dissociated from muscular contraction in the isolated rabbit heart. Coronary flow and oxygen consumption were determined in these hearts in an Anderson apparatus, with temperature, perfusion head, cardiac work, and heart rate maintained at constant levels. When magnesium was completely substituted for calcium on a molar basis, the contractions began to weaken, and a transitory increase in coronary flow was seen. As the contractions ceased, coronary flow diminished to below the control level. The heart stopped in diastole, but the electrocardiogram continued essentially unchanged. It was impossible to tell from inspection of the electrocardiogram whether the heart was contracting or not. Addition of calcium to the solution resulted in resumption of mechanical contraction; coronary flow increased but did not reach control values. The coronary flow appeared correlated more with oxygen consumption than with the state of the heart; even though the hearts were stopped in diastole, flow fell.

The oxygen consumption in the electrically active, mechanically quiescent heart was 1.6 ± 1 ml. per 100 Gm. per minute, and 3.0 ± 1 in the contracting heart. The oxygen cost of the processes of electrical activity and of basal requirements was thus shown to account for half the energy cost of the beating heart.

High-Dosage Steroid Therapy of Sydenham's Chorea

Irving G. Kroop and Nathan H. Shackman, Brooklyn, N. Y.

Eleven consecutive moderate to severe attacks of Sydenham's chorea were treated empirically for 4 to 9 weeks with a daily dose of 200 to 600 mg. cortisone, or 100 mg. Meticorten. This dosage was much higher than dosages previously reported to have given equivocal improvement in chorea. Motor function, after 1 week of hospitalization, served as a baseline for judging the effects of treatment. Serial motion pictures were an objective record of early, unequivocal and significant improvement of motor function after 2 to 23 days of treatment (average 8 days). Complete disappearance of purposeless movements occurred within 12 to 36 days (average 25 days). There were no serious complications of treatment.

The variability of chorea, the small number of cases treated and the lack of an untreated control group preclude a valid statistical appraisal. However, our observations suggest that high-dosage steroid therapy may prove significantly effective within 1 week in the severe case of chorea.

Clinical data from the literature on fever therapy of chorea also indicate a favorable immediate effect and a shortened course of the disease, similar to our steroid treated cases. This suggests a similarity in the mechanism of action of high pharmacologic dosage of steroid (much higher than the amount produced by a maximum stress reaction) and the mechanism of action of fever therapy.

Diurnal Serum Triglyceride (DST) Levels as Altered by Dietary Fat Intake

Peter T. Kuo,† and John C. Carson, Philadelphia, Pa.

A high postprandial triglyceride level has been shown to induce a number of undesirable physiologic effects. Postabsorptive lipemia can be minimized by reducing dietary fat intake, but an increase in serum triglyceride level was observed in 20 per cent of patients on a rice diet. Serum triglyceride, phospholipid, and cholesterol were determined at 2-3 hourly intervals for 24 hours. Diurnal serum triglyceride (DST) curve was plotted in each of 6 patients while: (1) on normal or 20 Gm. fat diet; (2) after 5-9 weeks of rice diet; and (3) 50-70 per cent corn oil formula diet. Two distinct types of DST curves were obtained in each of these patients following: (1) normal diet and corn oil feeding, when their DST curves showed 2 postprandial peaks, at 2-4 and 10-12 p.m. respectively, that dipped rapidly and were maintained at low levels until breakfast; (2) on fat restriction, when their DST curves showed a single and smaller peak, either in early afte-

noon or from 8 to 10 A.M. DST curves of 2 patients on a 20 Gm. fat diet were similar to those on high fat except that the 2 postabsorptive periods were low. No marked fluctuations in the serum cholesterol and phospholipid levels were observed. These observations show that dietary fat intake can profoundly influence the DST curves. With fat restriction, some patients may show an increase in the fasting serum triglyceride level but their postabsorptive and average values are generally lower than on high fat feeding.

Thyroid Function in Euthyroid Patients with Paroxysmal Atrial Arrhythmias

George S. Kurland, Arnold Golodetz, and A. Stone Freedberg, Boston, Mass.

Further evidence of the possible importance of the thyroid hormone(s) in the pathogenesis of cardiac arrhythmias has been obtained in a study of 39 patients with supraventricular tachycardias. Thyroid function was evaluated by clinical appraisal and laboratory tests, including basal metabolic rate, protein bound iodine, and I^{131} thyroid gland uptake. All patients were considered euthyroid by these standard parameters. In 11 such patients, on the other hand, following the infusion of I^{131}-labeled thyroxine, the half-time of disappearance (mean 5.7 days, S.D. .52) was significantly different from the normal (mean 7.2 days). The percentage turned over (12 per cent per day) and the values for average thyroxine distribution space (12.2 liters) and for micrograms of thyroxine degraded (84 μg. per day) were also elevated as compared to normal subjects.

The 2-hour red blood cell uptake of I^{131} tri-iodothyronine from whole blood in the 39 patients averaged 17.5 per cent (normals average 13.9 per cent). Abnormally high values were obtained in 12 of 26 patients with atrial fibrillation, whereas uptakes were abnormally high in only 3 of 11 patients with atrial tachycardias.

Five such patients, 4 with frequent uncontrollable paroxysms of atrial fibrillation and 1 with recent prolonged atrial fibrillation, were treated with large doses of potassium iodide. In each case, improvement resulted. In 4 of the 5, paroxysms of fibrillation became much less frequent; in the fifth, chronic fibrillation continued at a slower rate. In 3, the cessation of attacks coincided with a decrease in the red blood cell uptake of I^{131} tri-iodothyronine.

Validity of a Constant Injection Method for Measuring Mitral Insufficiency

William W. Lacy and Elliot V. Newman, Nashville, Tenn.*

The purpose of this work was to test a mathematical theory and method of measuring mitral insufficiency.

Constant injection indicator dilution methods are applicable to the determination of a combination forward and backward flow and would avoid the necessity of measuring volumes with their attendant errors. If, in the presence of mitral insufficiency, an indicator is injected at a constant rate into the ventricle and the concentration of indicator in the auricle and aorta are continuously recorded, the concentration at both sites will rise to an equilibrium value at a rate governed by flow-volume relationships. At equilibrium (recirculation excluded), however, the concentrations are directly related to flow and independent of volume; dye entering the auricle (concentration in ventricle $\times$ insufficiency) must equal dye leaving the auricle (concentration in auricle $\times$ forward flow and insufficiency).

$$\text{Therefore, insufficiency} = \frac{\text{forward flow}}{\text{conc. in vent.} - \text{conc. in aur.}}$$

Using constant dye injection, this method was examined in a mechanical model in which forward flow and insufficiency were known. The effect of inconstant mixing in the ventricle and a pulsating system on equilibrium concentration was minor and forward flow could be calculated within ± 5 per cent at flows from 1,200 to 2,400 ml. per minute. Calculation of insufficiency was greatly influenced by position of the auricular sampling catheter. Reliable measurements (+10 per cent when insufficiency equals half forward flow) of insufficiency were obtained only when the catheter was positioned at the mitral valve orifice and mean diastolic concentration measured.

The information acquired from the model can serve as a guide to the application of this method in animal and man.

Rate of Secretion of Aldosterone by the Adrenal Cortex in Normal Man and in Patients with Heart Failure, Nephrosis, and Cirrhosis

John H. Laragh, Stanley Ulick, and Seymour Lieberman, New York, N. Y.*

Information concerning the factors regulating aldosterone secretion has been based on measurement of the small fraction of hormone excreted unchanged. One cannot, however, be certain that urinary aldosterone accurately reflects adrenal production when individuals are compared who may exhibit different rates of inactivation and excretion.

A procedure has been devised which provides a precise estimate of the amount of aldosterone secreted by the adrenal glands. The technic utilizes

a recently isolated tetrahydro metabolite of aldosterone which occurs in urine in larger amounts than aldosterone itself. One microgram of tritium-labeled aldosterone is injected intravenously and the metabolite is then isolated from the subsequent 24-hour urine. Isolation involves 3 chromatograms and the formation of a C^{14} triacetate of the tritium-labeled metabolite. The amount of aldosterone secreted is calculated by dividing the total counts per minute injected by the specific activity of the urinary metabolite. The validity of the procedure has been verified by recovery experiments, in which known increments of aldosterone were administered.

With this technic, 2 normal subjects have been found to secrete 230 and 250 μg. per day of aldosterone. With sodium depletion, the secretion rate rose to 930 μg. per day and with sodium feeding it fell to 51 μg. per day.

Marked hypersecretion of aldosterone has been demonstrated in hepatic cirrhosis with ascites and in nephrosis. Repeated observations in a patient with cirrhosis on a metabolic regimen demonstrated a secretory rate of 2,000 μg. of aldosterone per day. The hypersecretion was not suppressed by sodium feeding. In contrast, 2 subjects with advanced congestive heart failure have repeatedly failed to exhibit hypersecretion.

Fetal Electrocardiogram in the Epoch from the Tenth to the Twentieth Week of Pregnancy

S. David Larks, Los Angeles, Calif.

On the basis of improved technic, it is possible to demonstrate large and unmistakably clear complexes associated with the beat of the fetal heart. In a search for the earliest possible demonstration of the fetal electrocardiogram, it is shown that fetal complexes can be identified at 11½ weeks embryologic age, counting from the presumed date of conception. These complexes are morphologically similar to those demonstrated in presentation by breech, suggesting that the fetus in these early weeks is indeed in the breech position.

It will be shown that the complexes reverse, to the form associated with vertex presentation, at 17-18 weeks in the usual case. It is also shown that the fetal electrocardiogram becomes large and clear rather suddenly in the vicinity of 20 weeks, so that diagnostic information should be available at that and subsequent weeks. Examples of the diagnosis of twin pregnancies by the fetal electrocardiogram at 16 and 21 weeks will be shown, as well as examples of cardiac abnormality in utero later in gestation. With this technic, it should be possible to diagnose not only multiple pregnancy, but also certain congenital abnormalities at 20 weeks or even earlier. It may be possible to demonstrate damage to the fetal heart due to disease or other processes at any time after the fetal electrocardiogram becomes demonstrable. An example of an abnormal fetal complex at 13 weeks will be shown.

Effects of Alterations of Systemic Pressure upon Arterial Oxygen Content in Patients with Congenital Heart Disease

Richard P. Lasser and Gabriel Genkins, New York, N. Y.

Studies of the effects of alteration of systemic arterial pressure upon arterial oxygen content have been made in a series of 30 patients, using a vasodepressor drug, amyl nitrite, and a vasopressor agent, l-norepinephrine. The lesions studied included tetralogy of Fallot, patent ductus arteriosus with pulmonary hypertension, and Eisenmenger's complex. These patients exhibited a significant decrease in arterial oxygen content, (0.9-8.4 vols. per cent), in response to a fall in systemic pressure. Such changes were not observed in 5 normal subjects, and in patients with isolated pulmonic stenosis or lesions with a left-to-right shunt in the absence of pulmonary hypertension.

A control group of 30 patients with mitral stenosis was used to determine the range of variability of serial arterial oxygen determinations. This range did not exceed 0.4 vol. per cent. In the test group, arterial samples were drawn to coincide with the nadir or zenith of systemic pressure, depending upon which drug was used, and simultaneous systemic and right ventricular pressures were recorded.

In patients with an abnormal aortic root, a rise in arterial saturation accompanied the elevation in systemic pressure caused by an intravenous infusion of l-norepinephrine.

The effect of these drugs is believed to be the result of variation of the systemic resistance to outflow from the right ventricle. The resistance offered by a pulmonic stenosis and or pulmonary hypertension is more fixed and variation in systemic arterial resistance allows a greater or lesser amount of venous blood to enter the aorta via the abnormal communication.

Cytological Differences of Lipid Metabolism in Human and Animal Arterial Wall

Abel A. Lazzarini† and Jere W. Lord, New York, N. Y.

The most frequently used method for the production of arteriosclerosis in the experimental animal is the feeding of pure cholesterol or diets rich in cholesterol derivatives during prolonged periods. Distinct vascular changes have been observed by

this procedure in rabbits, guinea-pigs and chickens, but there were hardly recognizable lesions in most carnivores and omnivores with moderate hypercholesterolemia unless appropriate hormonal treatment was also instituted.

There are, however, serious objections to attempting to identify human spontaneous arteriosclerosis and experimental cholesterol atherosclerosis based on the difference of types of histopathological changes in man and animal.

The purpose of these studies has been to reproduce with the utilization of aqueous microemulsions of cholesterol and neutral fats, the factors involved in the pathologic deposition of lipids in experimental and clinical arteriosclerosis, lipoidosis and cholesterolosis in vascular cells growing in vitro. A tissue culture technic was developed for the preparation of cell cultures of human and animal intimal cells, maintained in chemically defined media.

Specific differences in lipid metabolism of human and animal arterial cells and the influence of donor age and sex were demonstrated by histologic and histochemical methods. The effects of estrogens, coenzyme A, vitamin D, heparin and other drugs on the absorption have been investigated.

Effect of Calcium on Membrane Potentials of Digitalized Frog Ventricle

John Lee, J. Walter Woodbury, Samuel E. Kirk, Gary B. Grant, Gerard G. Randolph, and Stanley C. Scheyer, Seattle, Wash.

Digitalization of frog ventricle causes an increase and then a decrease in transmembrane action potential duration (T_{ap}). These electrical changes have been attributed to an inhibition of the active transport of Na^+ and K^+ resulting in changes in the internal concentration of these ions. Since it is known that the action of the cardiac glycosides depends on Ca^{++}, the effects of Ca^{++} on the digitalized heart were studied by means of microelectrodes placed in isolated, perfused, and driven ventricles. Transmembrane potentials recorded when the tissue was in various concentrations of Ca^{++} with 0.5 mg. of digitoxin per L. were compared with records obtained with identical but drug-free perfusates. With normal Ca^{++} (1.07 mM per L.), digitalization proceeds gradually, and marked shortening of T_{ap} occurs in about 3 hours. Doubling external Ca^{++} decreases the digitalization time to about 1 hour. With Ca^{++}-free perfusion, none of these typical effects occurred in a 2-hour period. Upon withdrawal of Ca^{++}, the action potential in a fully digitalized heart reverts to normal in less than 1 minute. The potentials obtained with low-Na^+ drug-free perfusates closely resemble potentials of the digitalized heart, and also revert to normal immediately after removal of Ca^{++}. Mechanisms of altered repolarization have been attributed to changes in membrane permeability to K^+ and Na^+ ions. The above data are consistent with the hypothesis that these changes in membrane ionic permeability depend upon Ca^{++} concentration. This effect indicates that calcium is essential to the functional structure of the cell membrane.

Acetylcholine-Induced Cardiac Arrest in Coronary Arteriography Studies

J. Stauffer Lehman, Fred S. Winter, William M. Lemmon, and William Likoff, Philadelphia, Pa.

With the need for satisfactory coronary arteriography becoming increasingly apparent, numerous efforts are in progress to evolve procedures for regularly effective radiologic visualization of coronary arteries.

This presentation deals with pharmacologically-induced cardiac arrest, effected immediately preceding or during the introduction of radiopaque medium into the coronary arteries, as a potential means of obtaining satisfactory coronary artery visualizations.

Acetylcholine-induced cardiac arrest during coronary arteriography has been studied by us in a series of experimental animals (dogs) and in 20 humans.

The acetylcholine has been introduced by both peripheral venous injection and direct introduction into the ascending aorta by catheter and by aortic needle puncture technics.

Placement of the opaque medium at the coronary ostia has been accomplished by either catheter aortography technic or by suprasternal needle puncture of the ascending aorta. With the latter procedure (suprasternal transthoracic aortography) the needle tip has been positioned near the aortic sinuses.

In dogs, acetylcholine-induced cardiac arrest has regularly resulted in improved demonstration of coronary arteries, as compared with the same opacification technics in which, however, cardiac arrest was not induced.

Our experience in 20 human cases has been somewhat more variable; in certain cases, excellent opacification was achieved, while in others less complete visualizations were effected.

Effect of Sitosterol on Survival and Recurrence Rates in Myocardial Infarction

John H. Lehmann and Blair M. Bennett, Seattle, Wash.

Much investigation has been accumulated concerning the depressant effect of sitosterol on various fractions of serum lipids, but little convincing evidence has been presented as to clinical benefit on manifestations of arteriosclerotic disease.

This is an interim report of a controlled long-term study on survivors of myocardial infarction. The material of this investigation consists of all subjects admitted to a general hospital since the start of its operation in January 1955. One hundred-sixty such patients were collected who survived their myocardial injury more than 30 days. Fifty-nine individuals were treated by one of the authors with sitosterol from 3 to 36 months. The control series comprised 101 patients treated by internists and practitioners with other methods.

As regards the age, sex, race composition and dietary management of the 2 groups, no significant differences were noted. Based on accumulated data of the first 3 years, a highly significant difference ($p = .0001$) was noted as to the influence of sitosterol on the survival of the patient.

While the number in the 2 groups is not yet large enough, nor the time interval long enough to permit a life-table or survivorship study, the favorable role of sitosterol administration over the period indicated appears to have been established in these trials.

Laboratory data exhibit a sustained lowering of serum cholesterol and low density lipoproteins of the group treated with sitosterol.

Cardiovascular Survey in a Population of Arizona Indians

Thomas F. Leo, John J. Kelly, Jr., Brooklyn, N. Y., and Howard A. Eder, Bronx, N. Y.

Five years of clinical observation of the White Mountain Apache Tribe have demonstrated no evidence of coronary artery disease in this community of 4,000 persons. We have attempted to study the effect of age on the ballistocardiogram in this environment where coronary disease is presumably unimportant as a cause of ballistocardiographic variation.

Over 110 ambulatory volunteers of each sex between 24 and 87 years were studied. No histories suggestive of coronary disease were encountered. Thirty-four per cent of all men and 29 per cent of all women had diastolic pressures over 95 mm. Hg. This prevalence of hypertension confirmed prior experience. Serum cholesterol values were 185.8 ± 40.0 mg. per cent for men and 197.4 ± 34.7 mg. per cent for women. A survey of food purchases by family groups and dietary habits of individuals indicates a lower fat consumption in this population than among white Americans.

Longitudinal and lateral ballistocardiograms were recorded by the method of Dock. Based on Brown's classification, the incidence of abnormalities increased rapidly in persons over 50. At 60 years, 6 hypertensive (85 per cent) and 5 normotensive (42 per cent) women had abnormal records (grade II or worse). Two normotensive men (20 per cent) at age 60 and 3 (60 per cent) at age 70 had abnormal records. These results resemble qualitatively those observed in normal white populations. Significant ballistocardiographic deterioration occurred after smoking in 16 men (16 per cent) and 10 women (20 per cent). These observations suggest that aging alone can be responsible for abnormal ballistocardiograms in the absence of coronary disease.

Three Cases of "Pulseless Disease"

Maurice H. Lessof, London, England

This report is based on 2 cases of large vessel thrombosis in young women, together with the necropsy findings in a third case. Only 1 of these 3 patients proved to have the obliterating brachiocephalic arteritis of Takayashu. One had an unidentified thrombotic condition of the large arteries, and the third had evidence of arterial occlusion associated with systemic lupus erythematosus. Blood flow studies in the limbs were helpful in defining the extent of peripheral arterial involvement even when symptoms were absent. In both patients studied clinically there was a diminished blood flow in the legs as well as in the arms.

Auscultatory and Phonocardiographic Findings in Ventricular Septal Defect

Maurice H. Lessof, London, England

Forty cases of ventricular septal defect were studied, including 13 with associated pulmonary stenosis, 7 with an atrial septal defect and 2 with aortic incompetence. The clinical and phonocardiographic findings corresponded closely with the results of catheterization or angiocardiography. A pansystolic murmur and normal second sound occurred with small defects and shunts below 2 L. per minute. With larger shunts, splitting of the second sound ranged up to 0.07 second, usually with normal respiratory variation. A mitral diastolic flow murmur was present in 12 cases with shunts of over 5 L. per minute and absent in patients with smaller shunts. Atrial systolic murmurs occurred only in cases with an associated atrial septal defect.

With pulmonary hypertension there was an intense, reverberating pulmonary second sound and close or reversed splitting. A pulmonary diastolic murmur was found only when the pulmonary diastolic pressure exceeded 30 mm. Hg. A marked decrease in the intensity of the systolic murmur indicated gross pulmonary hypertension and a diminishing blood flow through the lungs.

In atrioventricular canal defects, intense systolic murmurs were recorded, often with distinct s-

toli murmurs in the mitral and tricuspid areas. Fix splitting of the second sound was the rule. Di olic and atrial systolic murmurs were commo

(nosed patients with associated pulmonary ste sis (Fallot's tetralogy) had no pulmonary sec d sound, but this returned after surgery. In acy otic cases with a good blood flow through the pul onary valve the pulmonary component of the sec d sound was usually present but diminished.

He odynamic Changes with Isuprel in Complete Heart l ck

l vid C. Levinson and Herbert Shubin, Los An les, Calif.

T o patients with complete heart block and cor ary artery disease were studied hemodynamicall before and after Isuprel. Neither of these pati nts, aged 63 and 69 years, were in heart failure.

Hemodynamic findings prior to Isuprel injection were: (1) ventricular rates 28 to 30 per minute; (2) elevated mean pulmonary artery pressures; (3) low mean brachial artery pressures; (4) elevated total pulmonary and systemic vascular resistances; (5) decreased cardiac indices; (6) stroke indices increased, but less than expected for otherwise normal hearts with these slow rates.

Isuprel in a predetermined dose was injected into the pulmonary artery via a catheter, converting 1 to sinus rhythm. In both cases ventricular rates increased 2½ times after Isuprel.

Although sinus rhythm was restored in 1 and complete heart block persisted in the other, hemodynamic changes were similar as follows: (1) cardiac indices rose greatly; (2) stroke indices were unaltered; (3) total pulmonary and systemic vascular resistances fell markedly although mean pressures were inconsistently altered; (4) arteriovenous oxygen differences diminished and venous oxygen saturations increased; (5) oxygen consumption indices were unaltered.

The marked reduction of vascular resistance with Isuprel in these cases indicates the reversibility of the increased vascular resistance found in complete heart block.

The primary beneficial effect of Isuprel in restoring hemodynamics toward normal was probably du to acceleration of ventricular rate.

Me surement in Man of Blood Flow through Broncho- lmonary Anastomoses

lbert E. Levinson, Boston, Mass., Leon Cudko iez, London, England, Walter H. Abelmann,† Re ert Jreissaty, and Gordon Katznelson, Boston, Ma s.

nastomoses between bronchial and pulmonary ci lations, and their enhancement in certain diseases, are known anatomically. Flow through anastomoses between bronchial vessels and the pulmonary arterial or venous circulation should produce an early discrete contribution to the indicator dilution curve obtained from the left atrium after injection into the left ventricle or aorta. It can be shown that the area under this early segment of the left atrial curve is proportional to the total bronchopulmonary anastomotic flow.

When normal flow was expected on clinical grounds or demonstrated independently (as the difference between simultaneously measured left and right ventricular outputs), left atrial curves following Evans blue injection into the ascending aorta revealed no early component or a small one. With enhanced bronchopulmonary flow clinically expected or independently demonstrated, a sizable early component was inscribed.

Quantitation of bronchopulmonary flow by this method involves assumptions which, if they cannot always be fulfilled, can usually be approximated. The formula is:

$$\dot{Q}_{B\text{-}P} = \frac{\dot{Q}_{LV}}{A_A / A_{LA}}$$

$\dot{Q}_{B\text{-}P}$ = broncho-pulmonary flow
$\dot{Q}_{LV}$ = left ventricular output
A_A and A_{LA} = areas under peripheral arterial and left atrial indicator dilution curves

Normal bronchopulmonary anastomotic flow in man, measured by this technic, is about 1 per cent of left ventricular output. With pulmonary disease flow may exceed 5 per cent of left ventricular output.

The principle employed here is applicable wherever tagged blood, soon after injection of indicator, empties into an untagged chamber for which a timed volume can be determined. This method, therefore, may be useful in estimating flow through other regional vascular beds, including the coronary.

Problems in the Repair of Atrial Septal Defects

F. John Lewis and Riccardo Benvenuto, Chicago, Ill.

During the past 6 years, we have done open operations for the repair of atrial septal defects in 68 patients. With the exception of those patients who had persistent ostium primum defects or complicating mitral insufficiency the clinical follow-up results have been excellent and postoperative cardiac catheterization has confirmed the clinical impression.

We have described the surgical anatomy of these defects and called attention, in particular, to the high type of defect—a defect not previously dif-

ferentiated from the foramen ovale defect, at least in the clinical literature. This high defect is invariably associated with partial anomalous pulmonary venous drainage and it has been the second most common type (12 of 68 cases). Recognition of some aspects of its anatomy facilitate diagnosis and repair. Repair can be hazardous because thrombosis of the anomalous pulmonary veins or superior vena cava may be produced. Experimentally we have worked out a technic to overcome this difficulty.

Patients with high pulmonary artery pressures, but without reversal of the shunt, withstood the operation fairly well (4 out of 5 survived). In order to try and solve some aspects of the problem in patients with even higher pressures and with reversing shunts we have worked out a technic that will allow slow closure of these defects over a period of weeks or months after the operation has been performed. This technic may also prove useful in the repair of ventricular septal defects.

Asymptomatic Myocardial Infarction: Observation of Five Nonfatal Cases Diagnosed by Routine Serial Electrocardiography in a Working Population

Howard A. Lindberg, Albert Poindexter, and Jeremiah Stamler,† Chicago, Ill.

During the years 1951-56, 9,192 annual medical examinations on 1,919 employees (about 90 per cent male), aged 40-64, were carried out. Forty-one known cases of nonfatal myocardial infarction were observed. Of these cases 5 (all males) were entirely asymptomatic, i.e., free not only of pain, but also of any other symptoms, insofar as could be elicited. They exhibited the following characteristics: A record of at least one normal electrocardiogram; observation in a subsequent periodic examination of an abnormal ECG pattern consistent with a definite diagnosis of myocardial infarction; stabilization with a recognizable infarct pattern on serial ECGs; complete absence of any ascertainable history of any symptoms. Of these 5 cases, 3 subsequently developed congestive heart failure; 2 remain asymptomatic. It is concluded that asymptomatic myocardial infarction is by no means a rare occurrence in middle-aged American males.

Endocardial Fibroelastosis: In Vitro Length Tension Studies of Affected Endocardium

Leonard M. Linde and Forrest H. Adams, Los Angeles, Calif.

Recent studies of patients with endocardial fibroelastosis have suggested that the pathologic physiology involves a splinting effect of the thickened endocardium. Interference with ventricular and atrial contraction has been demonstrated angiocardiographically. In an attempt to understand further this internal cardiac splinting, in vitro length tension studies were performed on the endocardium and myocardium of 3 patients who died of fibroelastosis and on 3 selected controls.

Fresh endocardial and myocardial tissue was cut and measured. One end of each specimen was held by a clamp while the other was secured to the writing arm of a kymographic drum. Varying weights were then added at known time intervals, and the resulting changes in length were recorded on the kymographic paper.

In the hearts with endocardial fibroelastosis, tension in grams per cubic centimeter increased greatly when endocardium or endocardium plus myocardium was subjected to stretching. There was minimal tension increase in response to stretching when myocardium alone from the same heart was tested. In the controls, the normal 1 cell layer endocardium offered no resistance to myocardial stretching.

These static length tension studies demonstrate that the abnormal myocardium in endocardial fibroelastosis develops greatly increased tension as it resists stretching. This coincides with loss of ventricular contractility and heart failure seen clinically.

Electrocardiogram During Open Heart Surgery

Leonard M. Linde, Eva M. Kavan, and James V. Maloney, Los Angeles, Calif.

The electrocardiogram was continuously recorded during the entire surgical procedure in 25 consecutive patients placed on a pump oxygenator of the Gibbon type. Ventricular septal defect was the most frequent abnormality, while other diagnoses included tetralogy of Fallot, transposition of the great vessels, aortic stenosis, and mitral regurgitation. A single bipolar lead was recorded similar to lead 1 of the standard electrocardiogram, with electrodes on each scapular area. Effects of various aspects of the procedure, prognostic and diagnostic significance of certain electrocardiographic changes were noted.

Marked tachycardia, ventricular premature contractions, and all degrees of heart block occurred at various times in the procedure, and did not seem related to prognosis. No difference was noted with various anesthetic agents, but the level of ventilation and depth of anesthesia did affect the electrocardiogram. Widening of the QRS complex and severe ST segment elevation or depression often preceded serious difficulty. Postoperative return of the electrocardiographic pattern to that observed preoperatively seemed to be the best prognostic sign. Further correlation was made of electrocardiographic changes, age, diagnosis, and various aspects of the surgical procedure.

This initial study suggests that interpretation of the continuous electrocardiogram during open heart surgery can be of help to the surgeon, the anesthetist, and the cardiologist. The derived information must be correlated with other parts of the clinical and laboratory evaluation.

Slowing of the Idioventricular Pacemaker by Sympathomimetic Amines

Arthur J. Linenthal, Paul M. Zoll, Raphael B. Reiser, Leona R. Norman, and Beverly A. Fordyce, Boston, Mass.

A pathologic or physiologic explanation can rarely be found for repeated Stokes-Adams attacks; neurogenic or humoral mechanisms by which ventricular slowing or standstill might be produced have not been recognized. In particular, sympathomimetic cardiac inhibition has been thought not to occur since epinephrine seemed only to accelerate the heart even after adrenergic blockade.

In dogs with surgically produced chronic complete heart block we have studied the effects of sympathomimetic amines on the independent ventricular pacemaker as well as on the sinoatrial rate, which in the past has been the primary indicator of chronotropic effects.

Epinephrine regularly accelerated the ventricle and elevated the blood pressure. After phentolamine, however, epinephrine lowered the blood pressure and slowed the ventricle. Similar reversals of the chronotropic actions of isoproterenol and levarterenol were observed on the ventricle, and of all 3 drugs on the sinoatrial pacemaker.

Methoxamine and "B.W. 45-50," 3,6 dimethoxy and diethoxy derivatives of β-phenyl-β-hydroxyisopropylamine, elevated the blood pressure and slowed the ventricle markedly. These actions were unaffected by atropine but were blocked by phentolamine. The same cardiac effects were observed with the 3-methoxy derivatives of epinephrine and levarterenol, which have been identified in human urine.

These observations are contrary to accepted theory in two respects: sympathomimetic cardiac stimulation can be prevented by adrenergic blocking agents, and the heart, like many other end organs, has sympathetic inhibitory as well as excitatory receptors. Furthermore, these observations suggest mechanisms by which Stokes-Adams attacks may occur.

Postmitral Commissurotomy Syndrome: Four-Year Clinical, Pathologic, and Serologic Study and Its Relation to Restenosis

Philip Lisan, William Likoff, Philadelphia, Pa., and Attilio Reale, Rome, Italy

A review was made of 78 patients who had commissurotomies for isolated mitral stenosis 4 years previously. Of these patients, 27 per cent (21), developed the postmitral commissurotomy syndrome for the first time as early as 1 month and as late as 17 months postoperatively. Over 80 per cent (17) of this group manifested the syndrome within 4 months following surgery, with 70 per cent (13) having multiple recurrent attacks varying from 2 to more than 5 times.

The most common clinical manifestations consisted of fever, pleuritic and pleuropericarditic pain, tachycardia and generalized malaise and myalgia. This was accompanied by pericardial friction rubs but with *no* pleural friction rubs or fluid. There were no characteristic changes in the electrocardiograms. No difficulty was experienced in differentiating the postmitral commissurotomy syndrome from the acute rheumatic state. This latter condition was encountered in 2 patients who manifested the typical clinical signs and symptoms.

Antistreptolysin and antihyaluronidase titers rose from 1 to 2½ fold in only 2 patients during the first 3 months postoperatively. All the atrial appendage biopsies were negative for reactivation of the rheumatic state.

None of the patients with this syndrome developed restenosis of the mitral valve within the 4-year period. The only 2 instances of restenosis observed in this group occurred in those patients who did not have the postmitral commissurotomy syndrome.

It appears from these observations that the postmitral commissurotomy syndrome is an early recognizable clinical state, not accompanied by specific serologic abnormalities and not followed by any unusual tendency toward restenosis.

Differentiaation of Congenital Interatrial Shunts from Rheumatic Mitral Valvular Insufficiency

Philip Lisan, Daniel Mason, and Gordon Bendersky, Philadelphia, Pa.

Surgical repair of interatrial septal defects has now become a reality with negligible operative mortality and complete elimination of this vascular shunt. Therefore, it becomes mandatory to establish an exact diagnosis of this congenital lesion alone, or in combination with rheumatic mitral valvular disease. In a large series of patients with interatrial septal shunts (particularly in the older age groups), it is demonstrated that, for many years, a large percentage were misdiagnosed as having rheumatic mitral insufficiency alone due to the presence of a systolic murmur at the precordium.

An analysis is presented of 90 patients with this congenital abnormality in an attempt to stress the important differential diagnostic criteria (clinical findings, radiologic, electrocardiographic, car-

diac catheterization, etc.). Of 63 patients between the ages of 18 to 55 years, there were 20 per cent (13) who gave reliable histories of the rheumatic state as a child, yet had an associated and dynamic interatrial vascular shunt. Most of these patients were still amenable to corrective cardiac surgery, which further emphasized the need for precise anatomical diagnosis.

Staphylococcal Subacute Bacterial Endocarditis

Philip Lisan, Joseph F. Uricchio, Daniel Marino, and William Likoff, Philadelphia, Pa.

Thirty-five cases of staphylococcus subacute bacterial endocarditis, occurring from 1949 to 1957, were reviewed. The ages ranged from 2½ to 70 years (mean of 37 years) and consisted of 20 males and 15 females. There were 4 patients with congenital heart disease, while the remainder had rheumatic heart disease. Of the latter, 50 per cent (16) had isolated mitral valvular disease (mitral stenosis and/or insufficiency), and 20 per cent (6) had aortic involvement alone.

Cardiac surgical procedures were previously performed on 54 per cent (19) of these patients. Subacute bacterial endocarditis occurred immediately following surgery in 40 per cent (7) cases with 47 per cent (9) developing the infection within 4 months of surgery.

Coagulase positive staphylococcus was the offending organism in 26 per cent (9), while 68 per cent (24) were coagulase negative. Of these, 37 per cent (13) were sensitive to all antibiotics with two resistant to all drugs.

The over-all mortality was 33 per cent (11), with death occurring 9 to 62 days after treatment was started. In 1955, there were 9 cases and 3 deaths; in 1956, 8 cases with 4 deaths; and in 1957, a total of 5 cases and 3 deaths. Prior to 1955, almost all the patients recovered. Those with isolated aortic valvular disease had a 67 per cent mortality rate as compared to 25 per cent in those with isolated mitral valve involvement, and 33 per cent in combined mitral and aortic valve disease.

Various antibiotic regimens have been reviewed.

External Phonocardiogram Compared with Intracardiac Phonocardiogram in Atrial Septal Defect

Chi K. Liu, Los Angeles, Calif., and Aldo Jacono, Chicago, Ill.

A comparative study between external phonocardiograms, pressure tracings from both sides of the heart, and intracardiac phonocardiograms has been made. The purpose of this study was to identify the site of formation of murmurs and their transmission, and the mechanism of splitting of the heart sounds.

External phonocardiograms were recorded in 16 patients with atrial septal defect, with or without partial pulmonary venous drainage into the right atrium. Intracardiac phonocardiograms were recorded in 6 of the 16 patients. In 1 of the 6 patients, a right-to-left shunt was observed. In patients with left-to-right shunt, the following observations were made:

1. The splitting of the first sound (1 case) is explained with delayed closure of the mitral valve and delayed opening of the aortic valve.
2. The systolic murmur is probably a flow murmur generated in the pulmonary artery, right ventricle and atrium. Its intensity is usually greater in the pulmonary artery.
3. The splitting of the second sound is due to delayed closure of the pulmonic valve, connected with prolonged systole of the right ventricle on account of increased flow.
4. An early diastolic murmur was recorded within the LV and at the apex. A mid-diastolic murmur was best recorded within the RV and (with decreased intensity) within the RA. The same murmur was recorded over the left sternal border.
5. A presystolic murmur was recorded within various chambers and over various areas.

An interesting case with right-to-left shunt was studied in detail. The probable mechanism of the modifications of the heart sounds and the cause of the murmurs has been discussed.

Clinical Effectiveness of Chlorothiazide

George W. Loomis and Robert L. Grissom, Omaha, Neb.

Serial observations of serum and urinary electrolytes, body weight, and intake and output were made in 8 hospitalized patients, 6 with congestive heart failure, 1 with cirrhosis and severe ascites, and 1 with severe hypertension. All but 1 had a moderate to marked natriuresis and chloruresis with a diuresis and weight loss. The single refractory case, a patient with congestive heart failure, was thought to have reduced cardiac output and glomerular filtration rate. She responded to intravenous aminophylline and meralluride with natriuresis and weight loss. In the patient with hypertension, there was potentiation of the hypotensive effect of mecamylamine, but initial natriuresis was not prolonged or marked. The potassium diuresis in these patients was directly proportional to the duration of chlorothiazide therapy and bore a rough inverse relationship to the excess of body sodium. Hypochloremia occurred in 6 instances, a mild elevation of CO_2 on 6 occasions, and hypokalemia in 5. None of these was severe enough to cause obvious refractoriness. The longest continuous course of chlorothiazide (12 days—2,000 mg.

per [illegible] hours) was in a cirrhotic and was associated with hypokalemia. Urinary values for titratable acidity, ammonia and pH and the serum pH did not confirm carbonic anhydrase inhibition.

Role of the Liver in Digitalis-Induced Electrolyte Shifts

Bernard Lown, Gerald H. Whipple, William C. Shoemaker, Boston, Mass., Louis C. Craig, Charlottesville, Va., and Samuel A. Levine, Boston, Mass.

Skeletal and cardiac muscle do not fully account for the rise in arterial K and fall in Na that accompany rapid digitalization. The participation of the liver in these electrolyte shifts was studied in 9 dogs. These animals had chronically implanted catheters in the hepatic artery, left common hepatic vein and portal vein, thus permitting physiologic studies of the hepatic circulation. Digitalization was carried to the end point of ventricular tachycardia by means of acetylstrophanthidin, first by way of a peripheral vein and then by the portal vein. Simultaneous blood sampling allowed determination of electrolyte gradient across peripheral muscle, splanchnic and hepatic circulations.

During the initial peripheral digitalization, an average of 0.77 mg. of acetylstrophanthidin was required. At toxicity, hepatic venous K exceeded simultaneous arterial and portal concentrations by an average of 0.6 mEq. per L. while the Na was diminished by 1.45 mEq. per L. During the second digitalization, performed transhepatically, an average of 2.0 mg. of acetylstrophanthidin was required for ventricular tachycardia. At toxicity, hepatic venous K had risen by 3.5 mEq. per L., while Na decreased by 9.6 mEq. per L.

In all animals, at toxicity the liver was discharging K and taking up Na. Hepatic venous K concentration rose as high as 9.8 mEq. per L. Liver flow studies permit quantitation of these shifts. The data suggest that the liver influences digitalis tolerance, both by changes in electrolyte levels and by metabolism or fixation of the glycosides.

Effect of Oxygen Administration on Various Forms of Cardiac Disease

Peter C. Luchsinger, Martin L. Stoker, James J. Leonard, Kenneth M. Moser, and Sol Katz, Washington, D.C.

Administration of oxygen to patients with congestive heart failure is generally accepted as a valuable adjunctive therapy. Combined cardiopulmonary studies were undertaken to ascertain the physiologic rational for oxygen therapy in various forms of heart disease.

Three groups totalling 60 patients were studied while breathing room air and again while inhaling 35 or 100 per cent oxygen mixtures. Group I included individuals with pure left heart failure (elevated wedge pressure). Groups II and III included patients with precapillary pulmonary hypertension, either at rest or exercise. Arterial pCO_2 was normal in group II subjects and elevated in those of group III.

Inhalation of oxygen-rich mixtures produced the following results: (1) cardiac output was unchanged in groups I and II, and increased slightly in group III; (2) right ventricular work was not widely altered in any group; (3) pulmonary arterial pressure was unchanged in groups I and II, but fell in group III; (4) full arterial oxygen saturation was achieved in almost all patients; (5) mixed venous oxygen saturation rose in all groups with the greatest increase occurring in group III.

These studies indicate that oxygen administration produces no hemodynamic improvement in patients with left heart failure or cor pulmonale without CO_2 retention. The only benefit derived by such individuals is an elevation of mixed venous oxygen saturation, indicating improvement in over-all tissue oxygen tension. Patients with cor pulmonale in whom CO_2 retention exists, show not only enhanced venous oxygen saturation, but also amelioration of hemodynamic abnormalities.

Mechanism of Production of Heart Sounds

Aldo A. Luisada and Rudolf Zalter, Chicago, Ill.

The mechanism of production of heart sounds was investigated in normal animals and normal human subjects by means of intracardiac pressure tracings, plus external phonocardiograms.

Selective phonocardiograms (medium and medium-high frequency bands) were recorded through various filters in man, together with low frequency tracings of the precordium, carotid and aortic tracings, and jugular tracings.

The following conclusions have been reached:

1. The *first sound* is made of 3 phases. The central phase of the first sound contains at least 4 vibrations which correspond to the motion of the 4 valves in the following order: mitral closure, tricuspid closure, pulmonic opening and aortic opening. Whenever one or more large vibrations correspond to the phase of ejection, they are likely to be of vascular nature.

2. The *second sound* is also made of 3 phases. The central and final phases correspond to closure of the semilunar valves and opening of the A-V valves, in this order: aortic closure, pulmonic closure, tricuspid opening, and mitral opening.

Pressure tracings in normal human beings, correlated with phonocardiograms, confirm the above interpretation.

The most important vibrations of the heart sounds are caused by sudden changes of pressure and the rate of change determines the type of frequencies composing each of these sounds.

Intracardiac phonocardiograms were recorded according to a new method from a high frequency strain gage channel. The medium and high frequency vibration of the gage were differentiated, amplified, and filtered, then recorded by the phono channel. This system allows one to register the vibrations of the blood within the various chambers without introducing any additional device into the heart.

Intracardiac phonocardiograms confirmed the above findings.

Pulmonary Pressure-Volume Relationships in Diseases of the Chest Wall

Harold A. Lyons and Er Yi Ting, Brooklyn, N. Y.

The mechanics of breathing are affected by disease of the chest wall. Lung compliances are frequently reduced. The change in the thoracic wall compliance and its contribution to the overall decrease in total pulmonary compliance needs to be measured to understand the physiologic disturbance.

Fifteen patients with skeletal deformities or respiratory muscle disease were studied. Kyphoscoliosis, thoracic trauma, postoperative thoracotomy, muscular dystrophy and sarcoid respiratory muscle involvement were the clinical diseases affecting the subjects. By use of the pressure-volume diagram of Rahn, the relation of the pressure to the volume was found. The curve is obtained by measuring the pressure exerted against a manometer at different lung volumes when all muscular activity is voluntarily suspended (P_R). This is the moment when the chest is at apparent rest. The lung pressure (P_L) at the same changes of lung volumes is obtained with an intraesophageal balloon manometer system. By subtraction of P_L from P_R, the pressure of the thoracic wall, P_C, is obtained. Since the relaxation pressure normally has only 1 position, and is changed only by differences in the tone of the thoracic wall or elasticity of the lungs, the alteration of this curve was found to be markedly affected in the patients studied. Analysis showed that the major disturbance was in the thoracic pressure curve. The relaxation volume of the chest approaches the relaxation volume of the respiratory system. This is a reflection of both the immobility of the chest wall and the reduced state of lung inflation. The lung pressure curve was found to be normal, although in some patients the thoracic pressure curve and the lung pressure curve were both abnormal. This is the first application of the relaxation pressure-volume diagram in the study of pulmonary disease. The cause of the reduced total compliance can be defined as being due to changes in lung elasticity, thoracic wall abnormality, or a combination of both.

Clinical and Pathological Study of Benign Intracardiac Tumors: Report of Successful Removal of a Myxoma of the Left Atrium

James R. Malm, John B. Henry, and Ralph A. Deterling, Jr., New York, N. Y.

Intracardiac tumors have become a surgical problem with the advent of safe open heart surgery. The experience with these cardiac tumors has been revised. There were 6 documented myxomas of the heart, 1 polyp of the mitral valve and 1 myxoma which was diagnosed by means of microscopic examination of a tumor embolus removed from the right femoral artery. The clinical course of these cases has been correlated with the tumor size and location. There were 2 patients who died suddenly following a change in position and 2 who had recurrent angina pectoris.

The gross and microscopic findings with special reference to the tumor pedicle have been considered. Detailed study of the junction between the atrial septum and the tumor show that the tumor does not deeply invade the septum, hence, resection of the septum is not necessary. Preliminary histochemical studies indicate a high acid mucopolysaccharide content in the ground substance of the tumor. Tissue culture of 1 myxoma revealed a growth of endothelial cells and fibroblasts. These findings have been studied in relation to the true nature of these tumors.

A successful removal of an 8 by 6 by 5 cm. myxoma of the left atrium by use of extra-corporeal circulation has been carried out.

Effect of Carbon Dioxide on the Pulmonary Vascular Bed

Felice Manfredi and Herbert O. Sieker, Durham, N. C.

The direct effect of alveolar oxygen tension on the pulmonary circulation has been demonstrated, but the role of carbon dioxide in changing pulmonary hemodynamics remains undefined. This study was designed to investigate the direct effect of carbon dioxide on the pulmonary circulation.

In 7 dogs, the exposed left lower lobe was ventilated by a respirator and perfused by a pump with blood drained from the right atrium. In this system, all factors capable of modifying vascular dynamics indirectly, such as cardiac output, intracardiac and intrathoracic pressures, airway resistance, and neurogenic factors were excluded or controlled. By using different respiratory gases and ventilation rates between this lobe and remain-

ing ung parts, it was possible to vary as desired CO_2 concentration in alveoli, pulmonary arterial and or venous blood of the experimental lobe.

In this lobe, perfused with normal blood, and ventilated with 10 per cent CO_2 which raised alveolar and venous blood concentrations of this gas, calculated pulmonary vascular resistance increased. For example, an average rise of 8 mm. Hg in alveolar and venous pCO_2 resulted in a mean elevation of pulmonary vascular resistance from .19 to .29 mm. Hg/ml./min. When the same lobe was ventilated with air and perfused with hypercapnic blood (pCO_2 = 70 mm. Hg), the pulmonary vascular resistance remained unchanged.

The data suggest that elevation of alveolar and pulmonary venous pCO_2 decreases blood flow in the involved areas by a direct, local mechanism, and diverts it to well ventilated segments. However, if alveolar pCO_2 rises rapidly in large areas, the increase in pulmonary vascular resistance may ultimately overload the right heart.

Limitations of Serum Enzyme Alterations in the Differential Diagnosis of Myocardial Infarction

Carlos F. Manso and Felix Wróblewski, New York, N. Y.

In an attempt to define the limitations of the use of serum enzymes in the differential diagnosis of myocardial infarction, the various laboratory and clinical factors which influence serum glutamic-oxaloacetic transaminase, malic dehydrogenase, lactic dehydrogenase and aldolase were studied. The metabolic handling of increased serum enzymes was evaluated by in vivo studies of intravenous injections of pure enzyme preparations, as well as extracts of cardiac, renal and hepatic tissue extracts.

Some of the physiologic and metabolic mechanisms involved in the limitations of serum enzyme alterations have been considered. Drugs including aspirin, codeine, and other opiates, Dicumarol, Tromexan, alcohol, chlorpromazine, sulfamethoxy pyridine, methyltestosterone and others result in elevations of the enzymes. Inasmuch as some or all of these drugs are used in the clinical setting of acute infarction, the influence of drugs on serum enzyme must be considered when enzyme alterations contribute in the differential diagnosis of infarction. Other states, including acute or subacute muscular, hepatic, pancreatic, renal, and hematopoietic diseases, may exist and be accompanied by serum enzyme elevations in a clinical setting in which the diagnosis of acute myocardial infarction may be considered. Shock with or without congestive failure resulting in hepatic necrosis will elevate some of the serum enzymes in the absence of cardiac necrosis. Subendocardial infarction may be accompanied by no serum enzyme changes, or exceedingly small or transient elevations. Clinical examples are to be presented to point up the limitations of serum enzyme alterations in the differential diagnosis of acute myocardial infarction.

Auricular Overloadings

Jorge Martens de Oliveira and Henry A. Zimmerman, Cleveland, Ohio

The auriculogram of 193 patients was studied. There were 41 cases of mitral lesions, 100 cases of congenital cardiac malformations and 52 cases of pulmonary disease. Hemodynamic and vectorcardiographic correlations were established. The following are conclusions:

1. Backward orientation of the P vector, with notching and increase in the duration of the P waves in the limb and precordial leads were the important findings for the diagnosis of left atrial overloading.

2. Correlation exists between the duration of the P wave and the anatomy of the left atrium.

3. Relationship between the degree of the amplitude of the P waves and elevation of the right auricular systolic pressures was demonstrated.

4. The influence of arterial desaturation upon the shape and the amplitude of the P waves in cyanotic cardiac malformations and chronic pulmonary disease is emphasized.

5. Pulmonary emphysema may produce gross changes in the auriculogram in the absence of any right atrial overloading.

6. The existence of combined auricular overloading may be suspected from the EKG: (a) in the presence of morphologic signs compatible with overloading of both auricles; and (b) in the existence of morphologic signs of left atrial overloading associated with a tendency of the AP to deviate to the right.

7. The vectocardiogram may add important information for the differential diagnosis of atrial overloadings: P loops with leftward and backward orientation, increased in width, and figure 8 loops are very suggestive of left atrial overloading. P loops with normal width, increased magnitude and a forward orientation are diagnostic of right auricular overloading.

Prophylaxis of Rheumatic Activity: Six-Year Study of 138 Rheumatic Children with Particular Reference to Auscultatory Findings

Daniel Mason, Ella Roberts, and Margaret M. Milliken, Philadelphia, Pa.

This report deals with the prophylaxis of rheumatic activity in 138 previous in-patients of a

hospital. All clinical and laboratory manifestations of rheumatic activity were absent at the time of the patient's discharge from the hospital to the follow-up clinic, and each patient was initially placed on daily oral prophylactic therapy. Very careful follow-up regarding faithfulness to therapy was observed.

Of these patients, 103 took penicillin daily; 8 took sulfadiazine (allergic to penicillin); 1 took 100 mg. of Achromycin (allergic to penicillin and sulfa); 13 took medication only intermittently; and 13 took none. Three patients were allergic to both oral penicillin and sulfa.

Of the entire group there were 6 recurrences of rheumatic activity and 2 were questionable; only 1 was in the prophylactic penicillin group.

Careful analysis of the changing auscultatory findings in the entire group was noted. Of interest was the increase from 14.7 per cent of potential heart disease patients in June 1952 to 30.6 per cent as of June 30, 1958, with a decrease in the number of patients with mitral and aortic valvular murmurs. In the prophylactic therapy group, however, there were some patients who developed additional auscultatory abnormalities despite absence of clinical signs of rheumatic activity.

Hypertensive Heart Disease in the Aged, 65 to 94 Years of Age

Arthur M. Master and Richard P. Lasser, New York, N. Y.

This report concerns characteristics of hypertensive heart disease in the aged (65 to 94 years). The group is selected and includes only ambulatory people, none ill or hospitalized. Comparisons have been made with findings in a control group of apparently healthy, aged persons studied similarly. The diagnosis of hypertensive heart disease (HHD) was based upon the physician's clinical evaluation; in all cases, evidence of involvement of heart, blood vessels or kidneys was present. Diagnosis was not based on the height of blood pressure alone.

Mean pressures, modal values and frequency distribution curves have been considered by sex and by 5-year age groups. Mean pressures of HHD group were: 65-69 years, males 184/101—females 191/99; 70-74 years, males 184/98—females 191/97; 75-79 years, males 182/94—females 183/94; 80-84 years, males 181/93—females 186/93; 85-89 years, males 171/88—females 183/93; 90-94 years, males 183/94—females 177/90.

Mean systolic and diastolic pressures of the HHD group were significantly higher than were the apparently healthy of both sexes. In the HHD group, female systolic pressures were significantly higher than males and diastolic pressures were similar.

The incidence of angina pectoris, myocardial infarction, previous congestive failure, enlarged heart, abnormal ECG and previous cardiovascular accident have been considered.

Statistical approaches were studied in an attempt to separate HHD blood pressures from those of apparently healthy people. It is thus hoped to achieve some rational basis for therapy of elevated blood pressure.

Correlation of Systolic to Diastolic Blood Pressure in the Healthy Aged 65 to 106 Years of Age

Arthur M. Master and Richard P. Lasser, New York, N. Y.

The correspondence between the systolic and diastolic blood pressure was studied in 5,619 apparently healthy subjects without heart disease: 2,925 males and 2,694 females, aged 65-106 years. An equation was established to predict the most common diastolic pressure for any level of systolic pressure, and vice versa. The limits of "normal" variation of this relationship was computed and a table of standards for "normal" pulse pressure in the aged was derived.

A linear relationship represented the most accurate expression of the systolic-diastolic correlation. Regression lines of "best fit" were determined by the method of least squares. Separate equations are necessary for each sex, namely, $y = .340x + 32.44$ for males, and $y = .292x + 38.85$ for females. Correlation coefficients were .64 for males and .60 for females. Limits of variability were taken as ± 1 standard error on either side of the regression line: males $\pm$ 9.85, females $\pm$ 10.98.

The data showed no differences by age between the 65-74 and the 75-84 year groups. Female systolic and diastolic mean pressures were significantly higher.

Our predictive tables will furnish a basis for evaluation of the correspondence of a systolic to a diastolic blood pressure and vice versa, and in identification of a diminished or excessive pulse pressure. For example, among females, systolic pressure of 150 mm. Hg was associated most frequently with a diastolic pressure of 82 mm. Hg; a diastolic higher than 93 or lower than 71 might indicate a circulatory or cardiac abnormality.

Clinical and Hemodynamic Features of Primary Myocardial Disease

Thomas W. Mattingly, Loren F. Parmley, and Donald Campbell, Washington, D. C.

Observations were made in a group of patients with such primary muscle disease as myocarditis, fibroelastosis and in a few with myocardial lesions associated with muscular dystrophies. All were

under 40 years of age when symptoms began.

One or more of the following clinical features were present at time of hospitalization: (1) congestive failure; (2) cardiomegaly; (3) arrhythmia; (4) conduction disturbances; and (5) auscultatory findings suggesting valvular heart disease. Cardiomegaly and congestive failure were the most frequent combinations. Arrhythmias and conduction disturbances were seen some time during their clinical course, frequently difficult to manage and often a terminal event. Auscultatory findings suggesting valvular heart disease due to valvular incompetence associated with dilatation of valvular rings often resulted in an initial erroneous diagnosis of rheumatic heart disease. The chief clinical feature differentiating myocarditis from fibroelastosis was the presence of thrombo-embolic episodes in the latter. The characteristics of the hemodynamic findings were: (1) elevation of the end diastolic pressures in the ventricles; (2) elevation of the pulmonary artery and capillary pressures; (3) elevation of the right and left atrial pressures when relative incompetence of the A-V valves was present; (4) low and fixed cardiac output and; (5) abnormal configuration of the intracardiac pressure curves. Angiocardiograms were of little aid, merely reflecting the delayed intracardiac circulation or in eliminating other lesions.

Careful evaluation of clinical features and hemodynamic studies established the diagnosis with a high degree of accuracy as correlated with necropsy studies. An occasional instance of constrictive pericarditis with cardiomegaly presents the most difficult diagnostic problem. Myocardial and pericardial lesions were found to coexist.

Effects of Intravenous Aminophyllin upon Coronary Hemodynamics and Myocardial O_2 and CO_2 Metabolism of Normal and Diseased Hearts

George M. Maxwell, Douglas H. White, Jr., Charles W. Crumpton, George G. Rowe, and Cesar A. Castillo, Madison, Wis.

Contradictory opinions exist concerning the action of xanthines upon the coronary vasculature. This study was undertaken to explore the effects of aminophyllin in normal and diseased persons.

Fourteen normals were studied. Control cardiac output (Fick) and coronary blood flow (N_2O Fick) were measured. Aminophyllin (250 mg.) was given into the coronary sinus catheter for over 20 minutes and the coronary blood flow and cardiac output remeasured. Appropriate control and experimental pressures were recorded.

Respiratory exchange increased significantly and was associated with an increase in total body O_2 extraction and CO_2 production. Mean values (control and drug) for heart rate were 80 and 78 per minute, for MABP 96 and 96 mm. Hg, and cardiac index 4.0 and 3.5 L. per minute per $M.^2$ Calculated total peripheral resistance increased. Right atrial, end-diastolic right ventricular, mean pulmonary artery, and pulmonary capillary pressures all declined significantly. The coronary blood flow decreased from 79 to 69 ml. per 100 Gm. per minute ($p < 0.01$). Thus the coronary vascular resistance rose as a factor of the unchanged MABP associated with the reduction in coronary flow. The coronary sinus O_2 content decreased by 18 per cent ($p < 0.05$). Thus the myocardial O_2 consumption was maintained in the face of a reduced flow by an increase in the O_2 extraction.

Similar studies were undertaken in patients with mitral valve disease, and cor pulmonale. Similar trends were observed.

Under the conditions of these experiments, 250 mg. of aminophyllin, administered intravenously, resulted in a significant increase in peripheral and coronary vascular resistance. Vasodilatation was observed to occur only in the pulmonary vascular system.

Chicago Rheumatic Fever Secondary Prevention Program: First Two Years' Experience

John McDonough, Oglesby Paul, Louis deBoer, and Joel Edelman, Chicago, Ill.

The Chicago Rheumatic Fever Secondary Prevention Program has as major aims: (a) establishment and maintenance of a rheumatic fever registry, (b) provision of chemoprophylactic drugs to registered cases unable to afford drugs on a continuing basis, (c) development of effective follow-up methods and (d) evaluation of reported recurrences. During 1956 and 1957, 2,521 cases were registered. Based upon reports received from physicians attending these cases, 70 per cent had either rheumatic heart disease or 2 or more major manifestations (according to the Jones Criteria), 23 per cent had 1 major manifestation, 2 per cent had questionable rheumatic heart disease without major manifestations, and 5 per cent had neither rheumatic heart disease nor major manifestations. At the end of the 2-year period, 170 cases had been removed from the registry because of death, incorrect diagnosis, moved out of the city, lost, etc. Of the 2,351 cases remaining in the registry at the end of 1957, 89 per cent were put on chemoprophylactic drugs at the time of registration, whereas 11 per cent were registered without chemoprophylaxis. Approximately 10 per cent of all cases remaining in the registry were delinquent from medical supervision by 6 weeks or longer at the end of the 2-year period and were being followed up. The remaining 90 per cent were known to be under medical supervision. There were 40 confirmed recurrent attacks of rheumatic fever during the 2-year period.

Studies on Collagen Structure

Edward Meilman, Paul M. Gallop, New Hyde Park, N. Y., Sam Seifter, Bronx, N. Y., and Susan Michael, New Hyde Park, N. Y.

Collagen has been degraded by purified collagenase from *Clostridium histolyticum*. The enzyme is free of nonspecific protease and peptidase activity; it does not attack casein, hemoglobin or various synthetic amino-acid esters and peptides. The enzyme appears to require a specific grouping present in collagen or gelatin.

The final degradation products from the collagen-collagenase reaction all have N-terminal glycine and average 5-6 amino acids in length. C-terminal analysis using the hydrazine method shows a wide variety of amino acids. Approximately 60 per cent of the glycine bonds in collagen are split by the enzyme and, since specificity is not conferred by the C-terminal end, an amino acid appears to be necessary in a position penultimate to the severed bond for enzymatic attack.

Kinetic studies of viscosity, optical rotation and end-group analysis using neutral soluble collagen indicate that collagenase degrades collagen initially into fragments of relatively small axial ratio (viscosity), but retains native configuration (high optical rotation). This indicates that the 3-stranded helical structure can occur only in disparate regions of the collagen molecule.

Hemodynamic Changes Associated with the Valsalva Manuever in Normal Adult Male and Female Subjects

Henry C. Mellette, Richard W. Booth, Joseph M. Ryan, and Edward J. Neth, Columbus, Ohio

Right atrial, brachial arterial and intraoral pressures were measured during the Valsalva maneuver (40 mm. Hg intraoral pressure held 40 seconds) in 10 subjects, (6 females and 4 males). Eight indicator dilution cardiac outputs were obtained in each subject as follows: (a) 4 interspersed controls; (b) at 5, 15 and 25 second intervals during straining; and (c) following strain release. From these data the following parameters were calculated: (a) pulse rate; (b) stroke volume; (c) pulmonary circulation time; (d) central blood volume; and (e) total peripheral resistance.

During straining, significant changes were observed as follows: (a) right atrial pressure rose to 40 mm. Hg; (b) arterial pressures showed the usual pattern described by others; (c) cardiac output decreased from 30 per cent to 50 per cent, despite pulse rate elevation; (d) circulation time increased; (e) central blood volume decreased and; (f) total peripheral resistance increased markedly. Females showed a greater magnitude of change than males in all cases.

At the time of release the following were noted: (a) right atrial pressure returned to normal; (b) arterial pressures showed the characteristic "overshoot;" (c) cardiac output in all females rose approximately 30 per cent above controls while males showed no significant change; (d) circulation time decreased; (e) central blood volume approached the normal; and (f) peripheral resistance returned to near normal levels.

It appears that: (a) strain produces definitely greater changes in females than in males; (b) blood flow increases in females upon strain release; and (c) a dissociation results between central blood volume and pulmonary circulation time.

Cause of Primary Hypertension

Milton Mendlowitz, Stanley Gitlow, and Nosrat Naftchi, New York, N. Y.

Studies on the digital circulation have revealed increased neurogenic vasoconstriction in primary hypertension. Since l-norepinephrine is the chemical mediator of sympathetic nerve discharge (Von Euler), this increased vasoconstriction could be caused either by increased production of l-norepinephrine at the sympathetic nerve endings because of increased neural discharge, or by increased vascular smooth muscle sensitivity to l-norepinephrine, or by both factors. Increased sensitivity to infused l-norepinephrine of sufficient degree to account for the increased vasoconstriction was demonstrated in the digital blood vessels of patients with primary hypertension. Similar increased sensitivity can be produced in normotensive subjects by premedication with cortisone, prednisone or ACTH and is also seen in Cushing's syndrome caused by an adrenal cortical adenoma or hyperplasia. This suggests that an enzyme responsible for the immediate pressor inactivation of norepinephrine is being inhibited by the adrenal cortical steroids, since the effect can be achieved within a relatively short time and without associated hypertension. Smooth muscle hypertrophy may play a secondary role later in the course of the production of this increased sensitivity by the steroids as well as in primary hypertension itself.

Since iproniazid failed to change the l-norepinephrine sensitivity of normal digital blood vessels, monamine oxidase is probably not the enzyme involved. It is suggested that perhaps O-methyl transferase (Axelrod) is the enzyme which is inhibited by the steroids and that a hereditary deficit in this enzyme system may be the initiating cause of primary hypertension. This would not preclude the addition of renal and arteriosclerotic factors as the disease progressed.

Fallibility of Oral Chemoprophylaxis in the Prevention of Streptococcal Infection and Recurrent Rheumatic Fever

Joseph M. Miller, Boston, Mass.

Several carefully planned prophylaxis programs, employing continuous oral sulfadiazine or penicillin, have documented the efficacy of these agents in preventing streptococcal infection and recurrent rheumatic fever among susceptible individuals. The present report aims to appraise the incidence of streptococcal infection and recurrent rheumatic fever under conditions of oral chemoprophylaxis which prevail more realistically in a general population lacking the constant supervision of a research study.

A retrospective survey was made of 68 ambulatory rheumatic children being currently followed in a clinic. Fifty-seven of these children were observed for at least 3 years and over half (36) were followed beyond 5 years. Definition of streptococcal infection was limited to elevations of antistreptolysin - O titer of at least 2 dilution increments. Oral prophylaxis, if taken, consisted of either sulfadiazine or penicillin.

During 4,473 patient-months of observation of these 68 patients, 48 streptococcal "breakthroughs" occurred among 35 patients allegedly receiving adequate chemoprophylaxis. Additional streptococcal episodes without associated antibody rise probably escaped detection. Six recurrences of rheumatic fever and 1 case of glomerulonephritis ensued following these streptococcal infections.

These results emphasize the greater fallibility of oral prophylaxis when research conditions are lacking. Of the several factors which may lead to prophylaxis failure, patient cooperation in taking an oral drug seems most capricious. The high recurrence rate of rheumatic fever which followed these streptococcal episodes illustrates the greater susceptibility of these patients and the liability inherent to oral drug administration.

Congenital Absence of the Pulmonary Valve: Clinical and Pathological Syndrome

Robert A. Miller, Harvey White, and Maurice Lev, Chicago, Ill.

Recently, we have had the opportunity of studying 5 children with strikingly similar clinical findings. Four have now come to postmortem examination. All of these children had x-rays, electrocardiograms, and angiocardiograms, and catheterization data was obtained on the 2 living patients. Clinical findings: The children were moderately cyanotic. There was a grade III systolic murmur and a long grade III blowing early diastolic murmur. The latter was heard best in the second left interspace. This murmur was "to and fro" rather than continuous. In each case a pulsating mass was noted during cardiac fluoroscopy in the region of the pulmonary artery. Angiocardiography revealed an early visualization of the aorta from the right ventricle and a huge aneurysmal dilatation of the pulmonary artery, involving the left main branch primarily and forming a golf-ball sized or sausage-shaped mass in the left chest. Cardiac catheterization revealed an infundibular pulmonic stenosis and a bidirectional shunt at the ventricular level. The aorta was entered from the right ventricle.

Postmortem findings were the same for the 4 patients that died: infundibular pulmonic stenosis, ventricular septal defect, an overriding aorta, and absence of any true pulmonary valve. We feel that these cases of tetralogy of Fallot with free pulmonary regurgitation and aneurysm of the pulmonary artery form a distinct clinical syndrome from which the clinician can suspect congenital absence of the pulmonary valve.

Pathogenetic Mechanisms, as Related to the Treatment of Cerebral Infarcts and Intermittent Focal Cerebral Ischemia

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The majority of patients with clinically significant cerebrovascular problems have intermittent focal ischemia, cerebral infarction or a combination of these conditions.

As new methods of treatment become available, it is important to decipher the type of pathology present and to determine the basic pathogenetic process in each patient's problem. Cerebral infarcts are commonly caused by thrombosis or embolism. The former is generally associated with atherosclerosis, but the "triggering" mechanism can be systemic hypotension, polycythemia, vasospasm and, less frequently, trauma, arteritis, carotid angiography or pathology in the aortic arch. Embolism is frequently secondary to atrial fibrillation or other arrhythmias, myocardial infarction with mural thrombosis, subacute bacterial endocarditis and, less commonly, cardiac surgery, atherosclerosis of the aorta, trauma and tumors. Evidence concerning the pathogenesis, diagnosis and various types of treatment of these disorders has been considered.

While intermittent focal cerebral ischemia is generally associated with atherosclerosis, the mechanism causing the attack is not known. Evidence concerning the relative importance of vasospasm, systemic hypotension, incomplete thrombosis and polycythemia in the genesis of the attacks and the results of treatment have been studied.

Electrocardiographic Changes in Pulmonary Embolism

Paul F. Miner, Denver, Colo.

The electrocardiograms on 44 cases with clinical descriptions of pulmonary embolism, which were confirmed by autopsy, have been reviewed. The average age of the patients was 64 years. The diagnoses of the chief associated diseases were coronary artery disease in 16 cases, emphysema in 5, rheumatic heart disease in 4, hypertension in 3, thrombophlebitis in 3, pulmonary tuberculosis in 3, calcific aortic stenosis in 2, carcinoma of prostate in 3, hypertrophy of prostate in 2, and 1 case each of pulmonary fibrosis, liposarcoma, fracture of hip, Kimmelstiel-Wilson's disease, cerebral vascular accident, parturition, and pernicious anemia, and in 6 cases no other diseases could be diagnosed from the charts or autopsy reports.

The majority of cases had sinus tachycardia but 7 had atrial fibrillation, 2 had nodal rhythm, and 1 had atrial flutter. There were 3 cases each of right and left bundle-branch block. The most common electrocardiographic findings have been investigated.

Difficulties in diagnoses were encountered when there was a pre-existing right or left ventricular hypertrophy. Vector analyses of the terminal portions of the QRS complexes appeared to be of value. The diagnosis of pulmonary embolism by the electrocardiogram must be individualized on the basis of the previous cardiac status.

Use of the Intracardiac Microphone in the Study of the Normal and Abnormal Cardiac Cycle

Howard L. Moscovitz, Ephraim Donoso, and Ira J. Gelb, New York, N. Y.

An intracardiac microphone provides additional information concerning basic mechanisms of valve motion and ventricular contraction since it detects vibrations at their site of origin and effectively excludes sounds from distant cardiac chambers.

The intracardiac first heart sound consists of 2 major components; the first coincides with atrioventricular pressure pulse crossover and the second with ejection into the great vessel. The interval between the two gives an accurate measurement of isometric contraction. Because of the elevated atrioventricular filling pressure gradient in mitral stenosis, that component of the first heart sound produced by ventricular contraction is widely separated from the delayed mitral valve closure sound. This provides an opportunity to compare the relative intensity of the sound produced by ventricular muscle contraction and that due to valve closure.

The intracardiac second sound frequently begins before the nadir of the incisural notch, indicating that its initial vibrations occur during protodiastole, prior to complete semilunar valve closure.

The fourth heart sound, generally attributed to atrial contraction, is often of greater intensity in the ventricle than in the atrium. This suggests that vibration of the ventricular wall may contribute more prominently to the "atrial sound" than heretofore postulated.

Flow murmurs, often undisclosed by conventional phonocardiography, can be demonstrated by a microphone in the aorta or pulmonary artery during the contraction which follows a frustrate premature beat. When the microphone is located in the atrium, murmurs accompanying premature contractions rarely reach comparable intensity, indicating that any atrioventricular valve insufficiency occurring during premature beats must be minimal.

Therapy of Human Thrombo-Embolic Disorders with Fibrinolysin (Plasmin): Clinical and Laboratory Evaluation

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An agent capable of acutely dissolving intravascular clot would represent a valuable addition to present methods of treating the thrombo-embolic disorders. Several substances with clot-dissolving potential are currently being evaluated. The present report summarizes the clinical and laboratory effects noted following intravenous infusion of the enzyme fibrinolysin (plasmin) in 66 patients with thrombo-embolic disease.

The study group included 33 patients with acute deep thrombophlebitis, 12 with pulmonary embolism, and 21 with peripheral, cerebral or coronary arterial occlusion.

Changes in various coagulation parameters were measured serially for 24 hours following infusion. Prothrombin time, prothrombin content, Ac globulin, proconvertin and plasma recalcification time showed minimal change after infusion of fibrinolysin in doses which markedly enhanced plasma fibrinolytic activity. Fibrinogen levels were slightly to moderately depressed by fibrinolysin therapy, the extent of decline being related to dosage. No hemorrhagic phenomena occurred in any patient, including 49 who were receiving anticoagulant drugs. Toxicity of the material was limited to a febrile response, occasionally accompanied by chills and nausea, which occurred in 31 patients.

Clinical observations indicated that fibrinolysin infusion leads to prompt subjective and objective improvement in patients with deep thrombophlebitis of less than 7 days' duration. No pulmonary emboli occurred in the 32 patients treated.

While individual instances of objective therapeutic benefit were encountered frequently among patients with pulmonary embolism and arterial

thrombotic phenomena, firm conclusions regarding the value of fibrinolysin in these conditions are not yet warranted.

Alterations in Cholesterol and Lipoprotein Partition in Euthyroid Adults by Replacement Doses of Desiccated Thyroid

Campbell Moses, Thaddeus S. Danowski, Pittsburgh, Pa., and Herman I. Switkes, Aspinwall, Pa.

Although a relationship between hypercholesterolemia and hypothyroidism has long been recognized, it has been generally assumed that thyroid deficits do not exist if the usual indices such as serum protein bound iodine, I^{131} trapping, and protein bound I^{131} conversion ratios are normal. However the possibility exists that some degree of unrecognized hypothyroidism may exist even when these indices are normal and this may contribute to the increase in cholesterol and alteration in lipoprotein partition that occur in aging but otherwise healthy adults.

To test this possibility full replacement dosages of desiccated thyroid, 2½ to 3 gr. per day, have been administered up to 10 months to aging diabetics and nondiabetics institutionalized for custodial care. Measurements of body weight, pulse rate, and blood pressure and analyses of the protein bound iodine, total and free cholesterol, phospholipids, and α- and β-lipoprotein cholesterols were made before and at regular intervals after beginning the experimental regime.

While maintaining a normal protein bound iodine level, statistically significant decreases in total cholesterol and β-lipoprotein cholesterol were found in the great majority of subjects. While there was considerable variation in the persistence of the hypocholesterolemic effect, the data indicate that even in subjects euthyroid by the usual indices, a thyroid deficit exerting considerable effect on the cholesterol-lipoprotein partition may be present.

Coarctation of the Aorta: Observations on Growth of the Anastomotic Site Following Aortic Resection in Infants

Arthur J. Moss, Forrest H. Adams, Bernard J. O'Loughlin, and Wilfrid J. Dixon, Los Angeles, Calif.

Observations were made in 5 infants on the growth of the anastomic site 2 to 4 years after surgical correction of coarctation of the aorta. At surgery, 4 were under 9 months, the youngest being 18 days. Observations were also made on 15 subjects from 2 days to 74 years of age to establish the average normal growth of the descending aorta. Systolic and diastolic measurements were made from biplane angiocardiograms in both groups. In the postoperative patients, the physiologic adequacy of the suture site was determined by intra-atrial blood pressure and pulse measurements.

In infants under 6 months of age, the aortic diameter at the diaphragm during systole averaged 6.7 mm.; at 3 to 4 years, 10.9 mm.; and in adulthood, 20.9 mm. Although anatomic stenosis occurred in 4 of the subjects studied postoperatively, physiologic obstruction was not demonstrated. Pulmonary hypertension was found in 4 of these patients.

Since physiologic obstruction was not apparent with an aortic diameter 55 per cent of the expected normal, and since the average diameter in children 3 years of age normally exceeds 50 per cent that of an adult, it was concluded that anastomoses performed at this age should remain functionally patent even with no future growth of the suture line. If surgery is performed during the first 6 months, a minimum of 30 per cent of the expected normal growth is essential for a permanently adequate lumen.

Effect of Morphine on the Serum Glutamic-Oxalacetic Transaminase (SGO-T) and Serum Alkaline Phosphatase (SAP) Activities of Normal Persons and Those with Gallbladder Disease

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Determination of SGO-T activity is widely used to confirm the clinical diagnosis of myocardial infarction. Biliary obstruction causes elevated levels of SGO-T and SAP. Since narcotics are known to increase intrabiliary pressure, and because most patients with suspected myocardial infarcts receive narcotics, the effect of morphine on SGO-T and SAP levels requires evaluation.

Thirty-four asymptomatic patients with normal fasting SGO-T and SAP values were given ¼ grain morphine sulfate subcutaneously and serial determinations done at 1, 3, 5, 8 and 24 hours. Normal range for SGO-T is 5 to 43 units (colorimetric) and for SAP 0.5 to 4.1 Bessey-Lowry units. Group I consisted of 34 patients with no known gastrointestinal pathology and normal gallbladder x-rays. No elevation of SGO-T or SAP followed morphine administration. Group II was composed of 10 individuals with gallbladder disease. Significant SGO-T elevations occurred in 4 of 6 patients with cholecystectomy, 1 of 2 with nonvisualization, and none of 2 with multiple gallstones and visualizing gallbladder. Four of the 5 patients with SGO-T elevations had concomitant increases of SAP. Highest values were reached at 5 or 8 hours, and moderate elevations persisted at 24 hours. Maximum SGO-T levels were 94, 124, 224, 300 and 903. Peak SAP values were 4.4, 6.1, 7.0 and 7.7 units.

It is concluded that SGO-T elevations should be used cautiously in confirming the diagnosis of myocardial infarction in cholecystectomized patients who have received narcotics. No morphine-induced increase of enzyme activity occurred in persons with normal cholecystograms.

Studies on Etiology of Hypoxia in Cardiorespiratory Disease, Shunting or Venous Admixture Versus Alveolar-Capillary Membrane Block

Hurley L. Motley, Los Angeles, Calif.

Studies employing graded levels of high oxygen breathing (32-40 per cent O_2 and 100 per cent O_2) in over 100 cases of chronic cardiorespiratory disease indicates that the etiology of hypoxia results from poorly ventilated alveoli or perfusion of blood through nonventilated or very poorly ventilated lung areas and intracardiac right to left shunts. An alveolar-capillary membrane block was not a significant factor in these studies. Oxygen unsaturation is one of varying magnitude and not qualitatively different. Breathing 32-40 per cent oxygen (increases inspired pO_2 over 70 mm. Hg) should overcome unsaturation from an alveolar-capillary membrane block, as the increased pO_2 tension is more than adequate to overcome the increased resistance for oxygen diffusion through the pulmonary membrane. When hypoxia is due to multiple small shunting at the alveolar level, the 32-40 per cent oxygen does not restore the saturation to normal, especially with exercise. Exercise increases the cardiac output with increased perfusion of blood through poorly ventilated or nonventilated lung areas, or intracardiac, as compared to selective perfusion at rest through better ventilated areas. Rest and exercise arterial saturation measurements on air and graded levels of high oxygen breathing provide information on pulmonary blood flow with right-to-left shunts in intracardiac defects. Breathing 100 per cent oxygen at rest obscures multiple small shunting at the alveolar level because of the large increase in the oxygen partial pressure in the plasma, although single or multiple large shunts are not obscured.

Control Study of the Treatment of Claudication by Arterial Infusions of Histamine

Isidor Mufson, New York, N. Y.

The basis for the continued success of arterial infusions of histamine in the alleviation of intermittent claudication arouses self-searching analysis. Discussing a patient's successful increase in walking distance from 2 to 15 city blocks without pain after treatment, his physician, a public health expert, raised the question whether suggestion rather than histamine was the basis for the help obtained. To settle this point, we set up a program in the clinic where 10 new patients received arterial infusions of normal saline without histamine, and all the personal attention and encouragement which clinic patients receive during infusions. All patients were separated from each other in curtained individual cubicles. None of these 10 patients had arterial pulsations except the femoral. Oscillometric readings were very low. Walking tolerances were recorded during each visit and compared finally with the original walking tolerance 1 week after the sixth and last infusion. To verify the etiology of their claudication as peripheral arterial insufficiency, those not helped during the control study next received arterial infusions of normal saline with histamine. Improvement in the walking tolerance was considered proof that the diagnosis was correct. Walking distances of the 9 patients not helped by normal saline were increased in varying degrees by histamine. These studies therefore proved that suggestion was not the basis for the marked improvement in walking tolerance which we and others obtained in 8 of every 10 patients receiving arterial histamine.

This presentation also affords the opportunity to reiterate the superiority of arterial histamine when compared with surgical methods currently publicized. It presents a greater opportunity for the successful alleviation of claudication not limited by the patient's general or peripheral status without morbidity or mortality.

Urea Excretion Studied by Stop Flow Analysis

Herschel V. Murdaugh, Jr. and Roscoe R. Robinson, Durham, N. C.

Stop flow analysis was performed in anesthetized dogs using the method of rapid serial collection of urine formed during a short period of ureteral occlusion during mannitol osmotic diuresis, preceded and followed by control standard clearance collection periods. Analyses for urea, exogenous creatinine, PAH, inulin, and urine pH were performed. Changes in urine potassium, PAH, and pH were used to distinguish proximal from distal nephron collections. The appearance of inulin injected into the renal artery prior to release of the ureteral occlusion defined the appearance of glomerular collections.

It was found that the urea clearance/exogenous creatinine ratio (C_{urea}/C_{cr} ratio) from the distal nephron collections increased to as high as 0.91 as compared with C_{urea}/C_{cr} ratios in the proximal nephron collections of 0.50 to 0.64. In 2 dogs whose control C_{urea}/C_{cr} ratios were high (0.70 to 0.81-1 dog urea loaded), a decrease in the C_{urea}/C_{cr} ratio to 0.50 to 0.53 was noted in the proximal nephron collections, in association with significantly higher C_{urea}/C_{cr} ratios in the distal nephron urine collections.

These findings would agree with the occurrence of urea absorption by the proximal nephron and urea concentration in the distal nephron.

Further Experiences with the Surgical Correction of Rheumatic Mitral Regurgitation by Cross Polar Plication

Henry T. Nichols and Joseph F. Uricchio, Philadelphia, Pa.

Cross polar plication (mitral annuloplasty) has been performed on 93 patients with rheumatic mitral regurgitation. The present report analyzes our experiences with the procedure.

The total mortality rate was 27 per cent. Five deaths were due to staphylococcal and pseudomonas septicemia. Technical errors, cardiac failure, ventricular fibrillation, and cardiac arrest accounted for the rest. All patients over the age of 50 succumbed.

The mortality rate was reduced to 9 per cent in 11 patients in whom partial heart-lung bypass was employed, but rose to 60 per cent in 6 cases in whom mitral annuloplasty was employed by an open method.

A long-term follow-up of 38 patients has been made. Two late deaths occurred due to hepatitis and cardiac failure. A critical appraisal of symptomatic pattern revealed benefit in over 84 per cent of the rest.

Phonocardiograms, taken before and after surgery, demonstrated a decrease or abolition of the systolic apical murmur in most cases. There was little change in the apical diastolic murmur or opening snap in those cases in whom these events were identified preoperatively. Striking changes in heart size were uncommon.

Left heart catheterization was carried out postoperatively in 15, but little alteration in left atrial pressure pulse curves could be identified. On the other hand, cardiac ventriculography (direct needle puncture opacification of left ventricle) revealed no reflux opacification of left atrium in 9 out of 10 studied after surgery by this method.

It is concluded that cross-polar plication represents a satisfactory surgical approach to the problem of rheumatic mitral regurgitation.

Constant Force and Constant Mass Calibration of UF-BCG

Jan Nyboer, Detroit, Mich.

Clinically, we believe that either the constant mass or the constant force of calibrated UF-BCG readily evaluates changes of mass movement of blood produced by aortic obstructive disease, aortic valvular disease and the effects of corrective arterial or valvular surgery of the aorta.

However, to obtain dependable calibration has been a major difficulty in repeated successful and meaningful recordings of low frequency ballistocardiograms on the same or series of subjects in health or disease.

Conditions of uniform total mass calibration may be obtained by loading of the pendulum or other UF-BCG with subject and sandbags to a predetermined given weight. In this type of loading one may also have uniform subcritical damping of the natural periodic swing if no change occurs in the length of the pendulum during progessive or serial study.

Conditions of uniform force calibration for either a lightly or heavily loaded UF-BCG may be obtained by flopping or spinning a given weight through a fixed distance and rate on a device or lever operated by a motor attached to the ballistic platform for the subject. It is necessary, however to adjust the final amplifier sensitivity control to effect a uniform recording of the swing amplitude for the given calibrating force against all loads observed. A final record of the ballistocardiogram is made at a proportionally augmented amplifier gain during a held breath of the subject.

In comparative study recorded by both constant force and constant mass calibration, the displacement ultra low frequency ballistocardiograms are essentially identical. This is true with respect to the character of the complexes and the degree of displacement observed regardless of the total mass being moved.

Character and Significance of Electrical Impedance Measurements Associated with Mass Movement of Blood

Jan Nyboer, Detroit, Mich.

Gross and pulsatile displacements of blood are measured by electrical impedance methods. A characteristic positive pulse of increased electrical conductance with systole is present over the lung, great vessel and peripheral locations. By further surface exploration a characteristic negative pulse of decreased conductance is present over atrial and ventricular locations during their respective systoles. These (volemic) findings are confirmed by simultaneous roentgenphotofluorokymograms through lung, great vessel and cardiac fields.

Hydrodynamic and impedance studies of pulsatile flow in a model indicate that total flow associated with each pulse may be derived accurately by extrapolation and computation of the end systolic slope as it projects linearly to intercept the line corresponding to onset of systole. The pulse volume reflects variations in storage of fluid against variations in peripheral resistance to outflow. The recorded volume pulse represents a

dynamic graphic analogue computation of an expanding tube with some characteristics of total fluid flow, arteriovenous storage and venous drainage with each cycle.

Thus, we believe that blood vessels have physical memory systems for the volemic hydrodynamic events occurring within the given segments.

Direct Measurement of Left-to-Right Shunts by Respiratory Analysis

John J. Osborn and Marion B. Macey, San Francisco, Calif.

Respiratory measurements have been made in patients with congenital heart disease using a multichannel recorder, pneumotachygraph, electronic integrater and a rapid response carbon dioxide analyser. From the record of a patient breathing room air at rest, the pCO_2 of the pulmonary vein can be measured from the "alveolar plateau" of pCO_2 during each expiration. In addition, the pCO_2 of the pulmonary artery can be directly measured using a method for rapid equilibrium modified from the original work of Haldane. In normal individuals, the pCO_2 of the pulmonary artery is essentially equal to that of the mixed venous blood. However, in patient with left-to-right cardiac shunts, the mixed venous pCO_2 is, of course, higher than that of the pulmonary artery (due to dilution with shunted blood which has been through the lungs). In patients with shunts, the mixed venous pCO_2 can be measured by a period of equilibration during which the patient is given known graded concentrations of CO_2 in the inspired air, until the blood on both sides of the lung is brought, for a short time, to be essentially identical for pCO_2 with the mixed venous blood. Thus, we can measure in the same patient and within 1 minute, the carbon dioxide concentration in each major section of blood: mixed venous, pulmonary artery, pulmonary venous (and hence also aorta). From these data, it is easy to compute the net shunt when present.

This technic is appealing because of its rapidity and ease of application. It can be carried out at rest and during exercise and even on infants. It may have considerable value as a screening test. However, patients with small shunts are still difficult to distinguish from some normals.

Cardiopulmonary Bypass Complicated by Fat Emboli: Experimental and Clinical Study

Guy Owens, Jesse E. Adams, and H. W. Scott, Jr., Nashville, Tenn.

Microscopic sections of brain, kidney and lung tissue from patients whose unexplained deaths occurred shortly following cardiopulmonary by-pass procedures, have revealed abnormally large amounts of coalesced fat within the capillaries.

Under certain conditions, similar findings have been produced consistently in experimental animals in which a filming type of oxygenator has been employed. The severity of the microscopic embolization appears to vary directly with the duration of the cardiopulmonary bypass. Insignificant fat changes occurred in animals subjected to by-pass procedures of less than 1 hour. Heparin levels above the standard range (3 mg. per Kg.) failed to prevent the occurrence of embolic fat. The addition of protamine to heparinized unoperated and cardiopulmonary by-passed animals indicated that fat embolization was not influenced by this agent.

Microscopic fat emboli were observed in tissues from dogs sacrificed 15 minutes following total replacement transfusions, with blood which had been oxygenated and circulated in the pump-oxygenator device for a period of 2 hours. The effects of oxygenation, changes in pH, CO_2 and other factors on the colloidal structure of blood following use of the pump-oxygenator device have been studied.

Preliminary Report on the Effect of Triamcinolone (Aristocort) in Edematous Patients

Robert G. Page and A. R. Lavender, Chicago, Ill.

Triamcinolone, a steroid with a 16-α-hydroxy group, has been reported to increase urinary sodium excretion in experimental animals as well as in patients who were being treated for a variety of diseases. The present study was undertaken to determine the effect of this steroid in edematous patients. Several, one nephrotic and the rest cardiac, were given triamcinolone in doses ranging from 4 to 64 mg. per day for different lengths of time. Urinary sodium, potassium and chloride were determined daily. Daily weights were determined when possible. Serum electrolytes were measured at different intervals.

There were no significant changes in serum values. The urinary response was variable. The most "beneficial" effect was seen in a patient who showed an increased secretion of sodium and potassium during treatment and there was a continuation of the natruresis following the discontinuance of the drug. There was a concomitant increase in the urinary sugar in this patient, a known diabetic. The increase in urinary electrolytes may have been secondary to this.

The majority of the patients showed a depression in urinary sodium output with little change in the potassium values. There seemed to be some correlation between the dose and the degree of depression. Some patients showed a rebound phe-

nor enon, i.e., an increase in urinary sodium following the discontinuance of the drug.

Alt ation in Serum Cholesterol and Lipoprotein holesterol by Nicotinic Acid

illiam B. Parsons, Jr., and John H. Flinn, Ma ison, Wis.

erum cholesterol levels can be reduced in most hy ercholesterolemic patients by administration of lar e doses of nicotinic acid in the presence of a nor nal diet. The reduction is most prominent in the β-lipoprotein cholesterol fraction, with increase in the α-i-lipoprotein cholesterol fraction. Nicotinic acid was given in doses of 3 to 10 Gm. per day in 60 patients for periods up to 2 years. Doses higher than 6 Gm. daily did not improve the results in refractory cases. Flushing and pruritus subsided rapidly in the early stages of therapy and did not interfere with therapy. No toxic effects were observed on hematopoietic, cardiovascular, renal or hepatobiliary systems. A battery of liver function tests and needle biopsies of the liver in 17 patients treated for longer than 1 year revealed no abnormality of hepatic function or morphology. Dryness of the skin occurred in 14 patients, 2 of whom experienced a brown rash in the axillae and at pressure points, but these reactions did not interfere with continuation of therapy.

Nicotinamide is ineffective in reducing serum cholesterol levels. This difference suggests that the action of nicotinic acid does not depend on methylation in the liver. Studies of urinary levels of metabolites of nicotinic acid and nicotinamide are incomplete at the time of submission of this abstract. Preliminary studies of T-tube drainage in humans suggest increased amounts of free cholesterol in the bile following nicotinic acid administration.

Studies in rabbits by 2 groups indicate that nicotinic acid protects not only against hypercholesterolemia but against aortic atheromatosis to a surprising degree. Insufficient time has elapsed to determine the possible effects of this therapy on the progression of atherosclerosis in human beings but a controlled study is in progress in our clinic.

Temperature Dilution Curves for the Detection of Cardiac Shunts

Milton H. Paul, Chicago, Ill., Abraham M. Rudolph,† and Maurice D. Rappaport,†† Boston, Mass.

A new method for the detection of intracardiac shunts in patients with congenital heart disease has been developed using the indicator-dilution principle in conjunction with continuous high sensitivity blood temperature measurements.

The rapid injection of 2-4 ml. of cold physiologic saline (5-10 C.) at various intracardiac sites results in peripheral arterial temperature dilution curves that are grossly indistinguishable from the conventional T-1824 blue dye curves. The resultant arterial temperature curves (peak temperature changes of 0.02 to 0.05 C.) have been continuously recorded by means of a resistance thermometer element incorporated in a no. 25 needle or in various thin arterial catheters.

The needle or catheter is inserted into an exposed artery during right heart catheterization and arterial dilution curves may be obtained at any point in the study by simply injecting cold saline through the catheter. Large injection cooling artifacts may mask the subsequent temperature dilution curve if the artery and thermal sensitive probe are too close to the vein carrying the intracardiac catheter (and cold saline). Advancing the thermal sensitive probe up the artery into a larger caliber vessel usually removes this artifact.

This method has the advantage over dye technics in that an unlimited number of determinations can be made in rapid succession without introducing a significant foreign material and there is no interference with subsequent spectrophotometric determination of blood oxygen saturation. Comparison of temperature dilution and dye dilution curves in the same patient indicates that there is no significant difference in the appearance time, peak time or gross curve contour. The technic has been particularly useful in the detection of the site of a right to left shunt during cardiac catheterization.

Criteria for the Recognition of Strictly Posterior Myocardial Infarction by Conventional Scalar Electrocardiography

Joseph K. Perloff, Washington, D. C.

Ten cases of strictly posterior myocardial infarction (1 autopsy proven), first suspected by initial 0.04 second R waves in V_1, were studied by conventional electrocardiograms, right anterior and left posterior thoracic exploring electrodes and vectorcardiograms, using the corrected orthogonal system of Schmitt-Simonson.

According to the data, the electrical manifestations of infarction in this location were (1) a 0.04 second initial R wave in V_1 and in contiguous right anterior chest leads with, in the acute phase, S-T segment depressions and upright T waves; (2) a 0.04 second Q area in the diametrically opposite region of the chest (between spine and left scapula); (3) a shift in mean QRS transition zone to the right because of loss of posteriorly directed QRS electrical forces; (4) frequent slurring of the descending limb of the initial R in V_1, indicating abrupt change in direction of the QRS vector loop at that point; and (5) no Q waves in any conventional lead unless contiguous portions of lateral or

††Deceased.

diaphragmatic ventricular wall were infarcted. Exploring electrodes and vectorcardiograms were of principal value in corroborating the diagnoses.

V_1 R waves of 0.04 seconds may appear under other circumstances such as: (1) right ventricular hypertrophy; (2) right bundle-branch block; (3) vertical electrical axes which manifest left posterior 0.04 second Q areas and diametrically opposite right anterior R waves of similar duration; and (4) the Wolff-Parkinson-White syndrome with an anteriorly directed delta vector. Attention to these differential diagnoses and to the foregoing electrical manifestations of strictly posterior infarction should facilitate its recognition in conventional electrocardiograms.

Auscultatory and Phonocardiographic Studies of Pure Mitral Insufficiency

Joseph K. Perloff and W. Proctor Harvey, Washington, D. C.

Acoustic manifestations of pure mitral insufficiency were studied in 22 patients. Twelve underwent cardiac catheterization. Ten diagnoses were clinical (1 autopsy proven).

The typical murmur was pansystolic, beginning during isometric systole, invariably enveloping aortic valve closure and radiating widely from cardiac apex to the base, axilla, and back. It occasionally waxed in latter systole (4 instances) probably because of increased turbulence caused by coincident filling of the left atrium from both pulmonary veins and left ventricle. In 2 instances, the murmur consisted almost exclusively of the late systolic crescendo.

In 8 patients, unusual semilunar valve asynchrony occurred, due to early aortic valve closure. In 4, the split second sound widened with inspiration, narrowed with expiration, but never became single. In the other 4, right ventricular failure prevented conversion of the inspiratory augmentation of right-sided filling into increased stroke volume. P_2, therefore, did not move and the split second sound remained fixed throughout the respiratory cycle.

A third heart sound commonly occurred (15 instances), probably due to the rapidity of atrioventricular (Y descent) filling in mitral insufficiency. In 3 patients it was followed by vibrations having the auscultatory quality of a short diastolic rumble, despite the absence of a mitral gradient.

In 4 instances an intravenous pressor amine was infused to increase regurgitation acutely by raising the resistance against which the left ventricle contracted. The regurgitant murmur increased markedly and the third heart sound increased in intensity and occurred earlier in diastole, reflecting the increased left atrial V wave and the increased rate of fall of the Y descent.

Effect of Closure of Patent Ductus Arteriosus on Pressures in the Aorta, Pulmonary Artery, and Left Atrium

Richard M. Peters, Ernest Craige, Daniel T. Young, and Robert Zeppa, Chapel Hill, N. C.

Elevated left atrial pressure may play an important role in the production of pulmonary hypertension in congenital heart disease with left-to-right shunt. A series of 9 patients with patent ductus, of whom 5 had pulmonary hypertension, was studied. During operation for closure of patent ductus, pressures were measured simultaneously in the aorta, pulmonary artery, and left atrium. These pressures were recorded with the ductus open and occluded, and again 5 to 10 minutes after operative closure of the ductus.

After closure, systolic and diastolic pressures in the pulmonary artery fell, and the aortic diastolic pressure rose. Before closure the pulmonary artery pressure curve was domed. There was a dierotic notch that occurred near the peak pressure followed by a slow fall to diastolic levels. Following closure, the pattern reverted toward normal.

All patients with pulmonary hypertension before closure had v waves reaching 25-30 mm. Hg, and the pressure descended to a minimum at y of 10-16 mm. Hg. Following closure, these pressures immediately fell toward normal. Before occlusion an apical mid-diastolic murmur was recorded by the phonocardiogram in the patients whose left atrial pressure fell only to 16 at y.

Conclusion: The limited volume of the pulmonary venous and left atrial reservoirs, together with the fixed area of the mitral valve, may be controlling factors which lead to pulmonary vascular constriction and ultimately to pulmonary hypertension in patients with left-to-right shunts.

Influence of Hyperthermia and Hypothermia on the Ventricular Fibrillation Threshold of Dogs

Clifford M. Phibbs and Lloyd D. MacLean, St. Paul, Minn.

Utilizing a precise, quantitative method, the influence of hyperthermia, hypothermia and coronary occlusion in these states has been determined in 20 mongrel dogs. The equipment used has permitted a single electrical stimulus of known current strength and known duration to be delivered to the heart at a known time in the cardiac cycle. The ventricular fibrillation threshold of a given dog is reproducible to within 1 ma. if repeat tests are done at one sitting or even on subsequent days.

Occlusion of the anterior descending branch of the left coronary artery in the normothermic dog lowers the fibrillation threshold from 1/20 to 1/3 of the control level. Hypothermia causes a pro-

sive decrease in the fibrillation threshold. This effect of lowered temperature is manifested even with a decline from 38 C. to 37 C. At 30 C., the threshold declines to half the normothermic level. Spontaneous fibrillation occurs regularly below this level or upon occlusion of the anterior descending branch of the left coronary artery at 30 C.

In contrast, hyperthermia to 40 C. causes a marked elevation of the ventricular fibrillation threshold. Furthermore, the threshold after coronary occlusion in the hyperthermic heart remains above the normothermic level and spontaneous fibrillation has not occurred. Data on blood pH, oxygen content, carbon dioxide content, and hemoglobin are known and comparable in the hypothermic, hyperthermic and normothermic dogs.

The implications of this study on current therapy of patients with acute myocardial infarct and of patients undergoing surgery for coronary artery disease have been considered.

Intravascular Catheter-Type Instrument for Recording Phasic Changes in Blood Flow

Heinz P. Pieper, Columbus, Ohio

A flowmeter for measuring instantaneous blood flow in large vessels is presented. The instrument uses the principle of a differential transformer with variable coupling, the signal of which is amplified by a carrier amplifier with phase sensitive rectification.

The flowmeter is connected to the tip of a catheter tube with a diameter of 4.2 mm. An umbrella-type device, operated from the external end of the catheter, spreads to a maximum diameter of 20 mm., and serves to center the flowmeter in the axis of the stream. The flowmeter has a natural frequency of 100 c.p.s. and has been carefully tested by means of an accurate sinusoidal pump up to a frequency of 30 c.p.s. Within this range the flowmeter shows a linear response to frequency, as well as a linear response to flow velocity.

In a series of experiments, the instrument was introduced into the ascending aortas of large dogs by the way of the carotid artery. Opening of the chest was not necessary. The records obtained were similar to those known from measurements taken with the electromagnetic flowmeter in the open-chest dog. The application of the instrument for diagnostic purposes, especially during open heart surgery, seems to be possible and is planned for the future.

P Wave, P-R Interval, P-R Segment and Q-T Ratio of the Normal Orthogonal Electrocardiogram

Hubert V. Pipberger and Herbert L. Tanenbaum, Washington, D .C.

The true beginning and end of electrical signals derived from the heart can be determined with greater precision by the use of simultaneously recorded orthogonal ECG leads. The present study involved measurements of normal ranges of P durations and amplitudes, P-R intervals and Q-T ratios. Schmitt's orthogonal SVEC III leads were used which have been shown to approach ideal in constancy of lead direction and strength. Tracings were analyzed from 133 subjects showing no clinical evidence of heart disease. Film speeds used were 118 and 224 mm. per second. The beginning and end of the waves was measured from the earliest and latest deflections, respectively, wherever these occurred in the 3 leads.

The findings were as follows: P wave duration, 0.102 ± 0.013 second; P-R interval, 0.135 ± 0.024 second; P-R segment, 0.047 ± 0.017 second; Q-Te, O.41 ± 0.03; Q-T ratio, 1.0 ± 0.07.

Most of these results and ranges differed considerably from those of previously reported studies. No single lead was sufficiently reliable for accurate time determinations.

The results were further analyzed by relating age and heart rates of the subjects to the P duration, P-R intervals and P-R segments respectively. Positive correlations were found only at the extreme ends of the distribution curves.

The results of the present study indicate that the electric events of the heart cannot be timed with satisfactory precision in single leads. The discrepancies between the presented mean results and ranges and the commonly accepted normal limits emphasize the need for a re-evaluation of normal electrocardiographic standards and at the same time for multichannel recording.

Potential Changes Attending the Excitation Process in the Atrioventricular Conduction System of Bovine and Canine Hearts

Raymond D. Pruitt, Hiram E. Essex, and Howard B. Burchell, Rochester, Minn.

In human and canine hearts, structures of the atrioventricular conduction system can be identified only by painstaking dissection. In the bovine heart, these structures are morphologically distinct and offer certain advantages to the study of potential changes attending their excitation.

Records made from the prenodal atrial fibers displayed a rapid succession of sharp deflections occupying the interval between 70 and 50 msec. before the onset of the QRS complex. From the head, the midportion and the tail of the atrioventricular node, monophasic or biphasic waves were recorded occupying the interval between 55 and 35 msec. prior to the onset of ventricular excitation. Vagal stimulation altered the form of these waves and increased their duration to as much as 80 msec. Retrograde conduction over the nodal tissues

induced by ventricular premature beats was attended by gross distortion of records of nodal potential. Common-bundle excitation produced a monophasic negative spike and bundle-branch excitation a biphasic RS spike, 3 or 4 msec. in duration, occurring 30 to 35 msec. before the onset of QRS. Purkinje spikes were recorded from the subendocardial layers at, or a few msec. before, onset of QRS. Rate of conduction through the right bundle branch approximated 1,500 mm. per second.

In studies on the canine heart, polyphasic complexes similar to those of the prenodal region of the bovine heart were recorded. Nodal potential did not assume the variety of forms seen at different levels in the bovine node. Common-bundle, bundle-branch and subendocardial spikes all were quite similar in form to those of the bovine studies.

Depressive Reactions in Hypertensive Patients

Richard M. Quetsch, Richard W. P. Achor, Edward M. Litin, and Robert L. Faucett, Rochester, Minn.

Of 387 resident patients with arterial hypertension who were studied during 1954 and 1955, 202 were treated with forms of *Rauwolfia serpentina*. In 53 (26 per cent) of the patients so treated, a depressive reaction developed, which was moderately severe or severe in 21 patients (10 per cent). In contrast, the comparable control group of 185 hypertensive patients treated otherwise produced only 9 instances (5 per cent) of depression, of which 6 (3 per cent) were classed as moderately severe or severe. No evidence was found for any relationship of depression to severity of hypertension, to drugs other than rauwolfia, or to lowering of the blood pressure. No correlation could be found between depression and age or sex or the presence of associated complicating disease.

Depression occurred in 11 (58 per cent) of the 19 persons who had a history of depression prior to beginning treatment with rauwolfia and in 42 (23 per cent) of the 183 patients without such a history. There was marked variation in the dose of rauwolfia tolerated, but no depression was observed in patients taking less than 0.2 mg. of reserpine daily. Although 32 (60 per cent) of the depressive reactions occurred within the first 6 months after the initial use of rauwolfia, six episodes (11 per cent) developed after 1 year of treatment.

Because of the frequency and severity of depressive reactions among hypertensive patients treated with rauwolfia preparations, indications for its use must be evaluated carefully, and whenever possible, use of the drug avoided.

Ventilatory Response to Carbon Dioxide in Patients with Congestive Heart Failure

Lloyd H. Ramsey, John H. Griscom, and James Snell, Nashville, Tenn.

The discovery of pulmonary vascular reflexes, normal to low carbon dioxide, and normal oxygen tension (Pa_{CO2} and Pa_{O2}) in arterial blood, has directed attention to reflex mechanisms as the cause for the increased minute ventilation (V_E) of congestive heart failure (CHF). However, it is unlikely that the complicated process of ventilation is completely controlled in the complex metabolic derangement of CHF by any single mechanism. In order to examine one of the chemical factors which might be unsolved, the ventilatory response of nine patients with CHF to the inhalation of CO_2 has been compared with 5 normal subjects.

Use of an open circuit method allowed the maintenance of normal oxygen tension in the inspired gas during a 20-minute equilibration period and 3-minute collection of expired gas and arterial blood while the subjects breathed room air, 2, 3, and 4 per cent CO_2. Pa_{CO2} was calculated from CO_2 content and pH and allowed determination of dead space (V_D) and alveolar ventilation (V_A).

The change in V_E for a given increment change in Pa_{CO2} was significantly greater in patients with CHF (95 per cent confidence level). However, the difference was primarily one of V_D since the difference in V_A was not statistically significant. The abnormal increase in V_D can best be explained by a relatively low pulmonary blood flow in relation to ventilation. This is an additional nonreflex effect of the abnormal pulmonary blood flow in CHF. The response of V_A indicates a continuing chemical control of ventilation in spite of the low Pa_{CO2}. The work required for this ineffective V_D may well be one of the factors responsible for the sensation of effort in breathing (dyspnea) in CHF.

Diffusion Characteristics of the Human Lung in Congenital and Acquired Heart Disease

John Rankin and Quinton C. Callies, Madison, Wis.

It has been shown previously that the diffusing capacity of the lung for carbon monoxide is dependent not only on the physical properties of the alveolar capillary membrane but to a comparable extent depends on the pulmonary capillary blood volume and on the rate at which erythrocytes within the pulmonary capillary bed take up CO. If the diffusing capacity of the lung for CO (D_L) and the in vitro rate of combination of CO with intracorpuscular hemoglobin are known for several different O_2 tensions, it is possible to assess the

relative importance of these factors and to determine the "true" diffusing capacity of the pulmonary membrane (DM) and the average pulmonary capillary blood volume (VC).

Studies were performed on patients with congenital and acquired heart disease in order to determine the reason for the marked variation in DL. Briefly the results were as follows: Diffusing capacity is affected significantly by variations in the pulmonary blood flow and in the volume of blood within the pulmonary capillary bed at any instant. For example: 1. In patients with uncomplicated atrial septal defects, DL is increased due to a proportionate increase in DM and VC occasioned by the tumultuous pulmonary blood flow. 2. With the development of pulmonary hypertension, DL decreases owing to a proportionate reduction in DM and VC. 3. In patients with mitral stenosis, DL may increase on account of considerable capillary engorgement. On the other hand, DL may decrease owing to a reduction in DM.

Combined Mitral Stenosis and Insufficiency Studied by Left Heart Catheterization

Elliot Rapaport and Harold G. Richman, San Francisco, Calif.

Seventeen patients with combined mitral stenosis and insufficiency in whom the predominant lesion was equivocal clinically were studied by left heart catheterization. Aortic output was calculated by the Stewart method following left atrial injection of T-1824. Regurgitant flow was estimated by the Korner-Shillingford slope method.

Left atrial pressure averaged 20 mm. Hg (range 8 to 31) and bore no relation to the severity of mitral insufficiency present. Mitral mean diastolic pressure gradients ranged between 3 and 23 mm. Hg (mean 12). Estimated regurgitant flow was 0 to 2.7 times aortic output. A positive correlation was observed between the magnitude of injection to sampling site volume (predominately left atrial) and the severity of mitral insufficiency. When the pressure gradients were related to mitral valve flow corrected for regurgitation, only 2 cases remained in the predominant stenosis range.

A correlation of hemodynamic data with clinical findings was attempted. A parasternal lift and opening snap were seen in almost all patients and thus appears to be of little differential value. An apical heave, markedly decreased or absent first sound at the apex, and giant left atrium by x-ray, were consistently associated with severe insufficiency. Surprisingly, electrocardiographic and/or vectorcardiographic presence of right ventricular hypertrophy, either isolated (2 cases) or as combined hypertrophy (8 cases), was seen in predominant insufficiency. It is postulated that elevated left atrial pressure present in these particular cases leads to increased pulmonary vascular resistance and resultant pulmonary hypertension similar to that which may occur in mitral stenosis.

Effects of Alteration of Renal Artery Blood Pressure and Pulse Pressure on Renal Function

Nancy H. Rausch and Walter E. Judson, Indianapolis, Ind.

Renal responses to acute reductions in pressures were measured in patients during resection of thoracic aortic aneurysms. During occlusion of the thoracic aorta, the blood flow and mean pressure of the distal aortic segment were controlled mechanically by perfusing it in a retrograde manner from either the brachial artery or the left atrium. During the bypass, with the mean arterial pressure in the distal aortic segment ranging from 40 to 65 mm. Hg, renal plasma flows (PAH) of from 0 to 80 per cent and glomerular filtration rates (inulin) of from 0 to 88 per cent of the preocclusion levels were ultimately observed. There was a concomitant reduction in urine formation and sodium excretion. With re-establishment of the aortic flow, there was a rapid return of these renal functions towards the control levels.

Similar pressure and renal function measurements were made in patients during occlusion of the aorta for surgical repair of coarctation. In contrast to the previous group, there were no appreciable changes in renal function associated with either no changes or sizable reductions in mean arterial pressure and in pulse pressure. Following release of the occlusion of the aorta, and after establishing pressures similar to those of the proximal aortic segment, there was little or no change in renal functions.

Conclusions

1. With acute reduction of renal artery, mean pressure and pulse pressure in patients undergoing resection of thoracic aortic aneurysms, a critical level for measurable renal function was observed.

2. Renal function appeared to be independent of the renal artery pressure changes observed during occlusion of the aorta for repair of coarctation.

3. The autonomous intrarenal adjustments observed with the alterations in renal artery pressure during and after occlusion of the aorta in patients with coarctation suggest that the extensively developed collateral anastomoses provide adequate perfusion pressure to the distal aortic segment.

Antifibrillatory Effect of Central Sedation in Acute Coronary Occlusion

William Regelson and Ferdinand S. Hoffmeister, Buffalo, N. Y.

The objective of the study was to determine the effect of tranquilization, analgesia, and anesthesia

on ventricular fibrillation in coronary occlusion.

Acute coronary occlusion was produced in dogs by drawing ligature ends tight 1 week after they had been carried through the chest wall and around the anterior descending ramus at its junction with the left coronary artery. Serial electrocardiographic and blood pressure tracings were obtained and mortality under varying conditions determined. The presence of complete coronary occlusion was verified by autopsy. The mortality of conscious nonmedicated dogs was 77 per cent (10/13). Ventricular fibrillation was found to be invariably associated with death. The ventricular fibrillation follows a short period of ventricular tachycardia, and occurs usually within 5 minutes following the sudden occlusion.

Reserpine, 25 μg. per Kg.; intramuscularly, 150 minutes prior to occlusion, prevented ventricular fibrillation and mortality was 25 per cent (3/12). Mortality of dogs given pentobarbital anesthesia, 25 mg. per Kg., was 0 per cent (0/6), and in animals given morphine sulfate, 8-10 mg. per Kg., intramuscularly, 30 minutes prior to occlusion was 0 per cent (0/4).

In dogs given chlorpromazine, 2 mg. per Kg., intravenously, immediately after occlusion following ether anesthesia, mortality was 30 per cent (3/10). However, in dogs given chlorpromazine (2-10 mg. per Kg.) without preceding ether anesthesia, death was 60 per cent (6/10).

It is concluded that central nervous system depressants increased significantly survival in dogs following acute coronary occlusion by suppression of ventricular fibrillation.

New Method for Intravascular Measurement of Instantaneous Linear Velocity and Volume Flow of Blood in the Intact Subject

A. MacDonell Richards and Henry L. Taylor, St. Paul, Minn.

A velocity probe has been devised based on the thermostromuhr principle. The probe measures 9 mm. in length by 1.9 mm. in diameter, approximately the size of a no. 7 cardiac catheter. It is easily fitted to the end of a double lumen cardiac catheter, allowing linear flow velocity and pressure to be recorded simultaneously with a multichannel direct writing recorder. The flow probe also indicates intravascular temperature. Blood at intravascular temperature driven by compressed air through a test chamber and right angle flowmeter permits in vitro calibration. The probe gives a positive signal for forward flow and a negative signal for reverse flow. The sensing elements respond to frequencies greater than 100 c.p.s.

Recordings of instantaneous linear velocity flow and intra-aortic pressure have been made from different points in the aorta of intact dogs with concurrent electrocardiogram and pneumotachygram. Simultaneous aortography allowed positioning of probe, calculation of cross sectional area, average linear velocity flow, and observation of turbulence. The mean flow velocity measured by the probe varied widely in the range of 30 to 0 cm. per second. Instantaneous velocity pulse contours recorded from different sites in the aorta and alterations produced by varying experimental conditions have been studied. The velocity flow measured by the flow probe was higher than that observed on aortography by an average of 15 per cent. A 10 to 15 cm. per second variation with normal quiet respiration was striking. Instantaneous blood volume flows were calculated under varying conditions.

Accuracy of Continuous Photoelectric Recording of Dye Curves in the Measurement of Cardiac Output

David W. Richardson, Eugene M. Wyso, Allen M. Hecht, Richmond, Va., and Donald P. Fitzpatrick, Providence, R. I.

Commercial availability of a photoelectric device (Colson) for continuous recording of varying concentrations of Evans blue dye in whole blood has simplified measurement of cardiac output by the indicator-dilution principle. Photoelectric recording has been criticized in principle because of the inhomogeneity of whole blood.

To evaluate the accuracy of photoelectric recording, 33 measurements of cardiac output by the direct Fick oxygen-uptake procedure were compared with estimates obtained by the dye-dilution method using Evans blue dye and a Colson densitometer, through which arterial blood was drawn continuously. Subjects were 23 patients with cardiovascular disorders. Average Fick cardiac index was 2.42 L. per minute per M.^{2} By the dye method, using intrathoracic injection, average cardiac index was 2.28 L. per minute per M.^{2} The 2 averages were not significantly different ($p > .3$).

Ability to estimate accurately cardiac output by antecubital vein dye injection would extend the usefulness of the indicator dilution method. In order to extend previous evaluation by other investigators, cardiac output, measured by arm vein injection, was compared with intracardiac dye injection in 21 patients. Average cardiac index calculated from arm-vein dye injection was 2.25 L. per minute per M.^{2} and was not significantly different ($p > .6$) from that obtained with intrathoracic dye injection.

Photoelectric recording of Evans blue dye dilution curves permits adequate estimation of cardiac output, simplifies methodology, and allows reduction in dose of dye required, so that determinations can be repeated rapidly without skin discoloration.

Cardiac output can be accurately measured by injection of dye into a forearm vein.

"Biologic" Fluctuation of Serum Lipoproteins

Arthur U. Rivin, Los Angeles, Calif.

Variations in serum lipoproteins as high as 100 per cent were noted when placebo treated survivors of acute myocardial infarction were studied at monthly intervals for periods up to 1 year. Of the 10 patients observed, 5 had no significant fluctuation. The other subjects showed substantial changes in both electrophoretically and ultracentrifugally separated lipoproteins. Thus atherogenic index changes occurred as follows: 65-89; 47-92; 54-70; 96-42; 152-80. Neither alterations in diet, weight, life situation, psychologic stresses nor amount of physical exercise appeared to be responsible. Although the causes for these observed fluctuations are not clear, the clinical implications are apparent. The physician must be slow to accept a single measurement as indicative of "atherogenic potential" or a single change as indicative of a "favorable" therapeutic result.

Increased Incidence of Coronary Heart Disease in Prematurely Castrated Women

Roger W. Robinson, Norio Higano, and William D. Cohen, Worcester, Mass.

Coronary heart disease is rare in premenopausal women. The increased incidence postmenopausally has been ascribed to decreased ovarian estrogen production. A disproportionate number of middle-aged women with coronary heart disease under our care had been prematurely castrated. These observations prompted an investigation to determine whether or not early castration plays a significant role in coronary atherogenesis. During the past 20 years, about 400 patients have undergone bilateral oophorectomy prior to age 45 at this hospital. Two hundred and four of these women responded to a request for clinical and laboratory evaluation. Of these, 130 without previous prolonged estrogen replacement therapy comprised the study group. A control group consisted of 135 women who had undergone hysterectomy without castration during the same period. The mean ages at operation and at recall for examination of the castrates and controls were nearly identical. Obesity was present equally in both groups. An apparent increased prevalence of hypertension in the castrates (65; 50 per cent) as compared with the controls (58; 43 per cent) was not statistically significant. The incidence of vascular retinopathy, cardiac enlargement, peripheral vascular disease, migraine, diabetes, thyroid diseases, gall bladder disease and miscarriages was practically identical in the 2 groups. Seventeen of the 130 castrates (13 per cent) were found to have coronary heart disease, in contrast to 6 of the 139 controls (4 per cent). This difference was highly significant, suggesting that estrogen deprivation after bilateral oophorectomy is associated with a subsequent increased incidence of coronary heart disease. Thus, early castration of women should be avoided unless specifically indicated.

Urinary Excretion of Magnesium in Renal Disease

Roscoe R. Robinson, Herschel V. Murdaugh, Jr., and Ernst Peschel, Durham, N. C.

That hypermagnesemia may develop during renal failure is well known. Few data are available describing renal patterns of magnesium excretion in kidney disease.

Simultaneous determinations of inulin and magnesium clearance (uncorrected for protein-binding) were performed in 20 patients with different types of renal disease, exhibiting varying degrees of renal failure. Subjects were maintained on regular hospital diets or diets restricted in salt and/or protein. No patients received elevated intakes of magnesium or drugs previously known to alter magnesium excretion.

A definite relationship was found between total serum magnesium concentration and a degree of reduction of GFR (C_{In}). All patients whose GFR was greater than 30 ml. per minute revealed normal serum magnesium values. Serum magnesium was significantly elevated in all subjects whose GFR was less than 30 ml. per minute with but 1 exception. This patient, whose serum magnesium was normal despite reduction of his GFR to 14 ml. per minute, had received oral chlorothiazide daily. Preliminary studies of the effect of chlorothiazide on the urinary excretion of magnesium showed that, in normal subjects, 0.5 Gm. chlorothiazide orally may increase the urinary excretion of magnesium twofold.

Analysis of the magnesium clearance data demonstrated that as the GFR decreased and total serum magnesium increased, the ratio C_{Mg}/C_{In} rose, while C_{Mg} and UV_{Mg} remained within normal limits.

These findings indicate that magnesium excretion in renal disease is not proportional to the apparent filtered load, and suggest the presence of a compensatory mechanism which operates to maintain the renal excretion of magnesium in advanced renal failure.

Method for the Induction of Intravascular Structures

Simon Rodbard, Buffalo, N. Y.

The growth of bridges and flaps has been induced in the lumen of arteries. Stainless steel wire or a

linen suture placed as a "violin string" in arteries of dogs or chicks became covered with endothelium in about 3 weeks. The tissue on the cardiad face of the suture remained thin for periods up to 6 months. By contrast, the tissue on the lateral and downstream faces continued to grow; in 3 months a thick pedicle of connective tissue was in evidence; in 6 months a coarctation-like stenosis of the lumen had developed. Other arterial modifications included hypertrophy of the upstream wall, thinning of the downstream wall, and realignment of the elastica, and the occasional development of aneurysms.

These vascular modifications can be explained on the basis of hydrodynamic forces. Thus, high pressures on the cardiad face compress the endothelium and inhibit growth. At the lateral and peripheral faces where the velocity is high, the reduced lateral pressure permits continued proliferation, even to the point of stenosis. The results demonstrate that the growth of intra-arterial structures can be induced by utilization of hydraulic principles. These principles may provide a basis for the plastic reconstruction of deformed vessels and valves.

Clinical Evaluation of Diethanolamine in Treatment of Hypercholesteremia

Dan C. Roehm, Nashville, Tenn.

In 24 hypercholesteremic patients, daily oral administration of .75 to 2 Gm. of the diethanolamine salt of the mono(d) camphoric acid ester of α-4-dimethyl-benzylalcohol (DEA salt) in divided doses, reduced significantly total serum cholesterol in all but 1 patient. Mean control cholesterol (modified Bloor) was 288.9 $\pm$ 25.1 mg. per cent. After treatment, mean values of 217.9 $\pm$ 14.5 mg. per cent were obtained for periods of from 3 to 18 months (average 8 months). The mean of the serum cholesterol differences was 71.0 $\pm$ 37.9 mg. per cent. Two, often more, control values in reasonable agreement at least 2 weeks apart, were required (2 exceptions). Any pretreatment value below 250 mg. per cent was held disqualifying. All laboratory estimations were performed on coded specimens by the same analytic chemist. No specimens were drawn less than 3 hours, and most were 5 hours after meals.

Intravenously, "DEA" elicits a characteristic biphasic action curve as exemplified by ester/total cholesterol ratios in 1 patient. Before DEA injection, 190/316, at 30 minutes 236/341, and at 60 minutes 146/301 mg. per cent values were obtained. (After 3 months, using the oral DEA salt, these values had reached 101/204 mg. per cent). This patient's control lipid values, his values 12 hours after infusion of 6.75 Gm. calculated as DEA, and after 5 weeks of 1 Gm. of daily oral DEA salt, were respectively for total lipids, lecithin, fatty acids, and neutral fats: 913, 806, 322; 200, 180, 150; 300, 280, 262; 400, 340, 105 mg. per cent.

The ethanolamines are extensively used in rendering soluble many medicines. This same property may explain the lipid effects in the body as well.

Correlation of Clinical and Experimental Phonocardiographic Criteria in the Diagnosis of Atrial and Ventricular Septal Defects

William M. Rogers, James R. Malm, Norman Thompson, James B. Harrison, and Ralph A. Deterling, Jr., New York, N. Y.

Interatrial and interventricular defects were created in dogs and direct phonocardiograms made over cardiac chambers and valves. Specific sound patterns were obtained for each defect. Atrial defects of 1 to 2 cm. in diameter produced an immediate dilitation and arterialization of the right heart. Extreme diastolic overloading to the point of failure occurred in the largest defects.

Characteristic murmurs appeared only after a recovery period, when diastolic volume decreased and systolic output increased. Phonocardiograms present a systolic murmur over the pulmonary valve and second sounds widely split through all phases of respiration, resulting from prolonged systole. The second component of this split sound arises from pulmonary valve closure. Its intensity varies with the degree of pulmonary hypertension and right ventricular systolic pressure. This second component of the split second sound and the pulmonary systolic murmur disappear with pulmonic valvectomy.

Interventricular defects maintained by a tubular prosthesis produce a systolic jet and thrill over the right ventricle opposite the defect. A characteristic coarse shunt murmur was loudest here. An additional pulmonary ejection thrill and murmur were present.

Twelve human cases of interatrial and interventricular defects were recorded by chest wall and direct phonocardiography before and after open heart repair.

The records are comparable in all respects to the experimental data. Interatrial and interventricular defects both produce a pulmonic ejection murmur but interventricular defects produce a shunt murmur which is dominant and characteristic. Phonocardiograms are reliable in differentiating between atrial and ventricular septal defects. Valuable information regarding size of shunt and degree of pulmonary hypertension have been obtained.

Pheochromocytoma: Evaluation of the Pharmacologic and Chemical Tests as an Aid to Diagnosis

Grace M. Roth, Eunice V. Flock, and Walter F. Kvale, Rochester, Minn.

Pheochromocytoma produces excess epinephrine and norepinephrine in varying amounts and hypertension, either sustained or paroxysmal with attacks, with hypermetabolism and disturbed carbohydrate metabolism. Because clinical signs and symptoms may be inconclusive, pharmacologic and chemical tests are employed as aids in diagnosis.

Precautions are necessary with all these tests. Sedatives produce falsely positive results with histamine and regitine, whereas antihypertensive drugs produce falsely negative results. However, cessation of sedatives for 48 hours and antihypertensive drugs for approximately 6 days will produce reliable results in regard to pheochromocytoma.

Use of chemical tests for pressor amines alone may be unreliable in the diagnosis of pheochromocytoma after administration of chlorpromazine, tetracycline and perhaps other drugs, for patients with azotemia, jaundice, and certain diseases such as lymphoblastoma and for patients receiving antihypertensive or vasoconstrictor drugs for such conditions as asthma or vasomotor rhinitis. However, cessation of drugs that influence the pressor amines for approximately 6 days will produce reliable results. Without stimulation with histamine, falsely negative results may occur.

Urine for catecholamine determinations should be collected after a spontaneous or induced attack. Even then normal levels have been found with proved pheochromocytomas. Patients receiving vasoconstrictor substances may have increased catecholamines without pheochromocytoma.

Tests performed were: 12,307 pharmacologic tests on 11,212 patients; 432 for plasma pressor amines on 313 patients and 113 for urinary catecholamines on 103 patients. We have diagnosed and removed pheochromocytomas in 60 patients. No untoward effects or deaths occurred during tests, operations or immediately after operation.

Fibrinolytic (Plasmin) Therapy of Experimental Coronary Thrombi with Alteration of the Evolution of Myocardial Infarction

Paul Ruegsegger, Irwin Nydick, Alvin Freiman, Albert V. P. Hutter, Nils Bang, Eugene E. Cliffton, and John S. LaDue, New York, N. Y.

The effects of the fibrinolytic enzyme plasmin upon experimental coronary thrombi and the evolution of myocardial infarction were studied in open chest dogs by direct coronary arteriography and histologic examination.

Coronary thrombi were produced by inducing a "hypercoagulable state" in an isolated segment of a major artery by a modification of Wessler's method. Rapid clot formation resulted from the intra-arterial injection of a mixture of blood and serum from the operated animal.

Serial arteriograms of the coronary tree were obtained by injection of Hypaque through a polyethylene catheter previously inserted into a tiny proximal side-branch of the artery under study. The presence of clots and their subsequent change in size were reflected by measurable arteriographic filling defects in the previously patent vessel. In 8 controls the thrombi remained stable up to 15 hours with an average clot retraction of 20 per cent. Spontaneous fibrinolytic activity in 1 control resulted in clot dissolution.

Lysis of coronary thrombi within 6-8 hours was achieved in 100 per cent of the treated animals by the intravenous infusion of plasmin.

An alteration in the natural evolution of myocardial infarction was definitely suggested as a result of the fibrinolytic state. Treated infarcts showed a marked decrease in capillary congestion, less interstitial edema and complete absence of capillary thrombi in striking contrast to the controls. These changes occurred even prior to complete lysis of the primary thrombus, suggesting that plasmin may penetrate the infarcts by collateral perfusion. This may be of importance in extending the viability of the ischemic myocardium. No evidence of myocardial damage due to plasmin was seen. Studies now in progress are dealing with late effects of rapid restoration of patency of the capillary bed.

Relative Significance of Heredity, Diet and Occupational Stress in Coronary Heart Disease of Young Adults

Henry I. Russek, Staten Island, N. Y.

Comparison was made of the hereditary background, health practices, diet, mode of life and sources of tension in 100 patients between the ages of 25 and 40 with established coronary disease and similar but unmatched control group of 100 normal subjects. Factors which appeared to differentiate the young coronary patient from the normal control were found in relation to heredity, diet, occupational stress and the use of tobacco. Emotional stress associated with job responsibility appeared far more significant in the etiologic picture of coronary disease than heredity or a prodigiously high-fat diet. Almost without exception, the young coronary patient was found to be an aggressive, ambitious individual who had lived beyond his normal capacity and tempo. Three out of every 4 in this group were working more than 60 hours per week or holding down 2 jobs. The

coronary patients were much more frequently addicted to the use of tobacco in excessive amounts but this is interpreted as an indication of heightened emotional tension rather than as an etiologic relationship. No significant differences were observed with regard to obesity or exercise in the coronary and control groups. It is apparent that re-orientation is needed in epidemiologic studies which ignore the profound effect of socio-economic stress on bodily function and human behavior.

Nitroglycerin and Other Nitrites in the Treatment of Angina Pectoris

Henry I. Russek, Staten Island, N. Y.

The comparative value of various nitrite preparations in the treatment of angina pectoris when administered by the oral or sublingual route was studied in 28 patients by means of the Master two-step test. Nitroglycerin, erythrol tetranitrate and triethanolamine trinitrate biphosphate were much more effective sublingually than when swallowed. Nitroglycerin and erythrol tetranitrate when administered sublingually are among the most potent of all prophylactic agents available for the treatment of patients with angina pectoris. Nevertheless, by the oral route their action is markedly reduced due to inactivation in the gastrointestinal tract. For similar reasons Nitroglyn (a sustained action oral preparation of nitroglycerin) exhibited limited responses even in large dosage. Triethanolamine trinitrate biphosphate was found to be relatively inert by the oral route and to possess weak vasodilator action by sublingual administration. Pentaerythritol tetranitrate, in contrast to other preparations, showed marked effect when swallowed, but little favorable response by the sublingual route.

While nitroglycerin is without equal for the acute attack, erythrol tetranitrate sublingually or pentaerythritol tetranitrate orally are valuable agents for prolonged prophylactic therapy in patients with angina pectoris.

Diagnostic Value of the Master Two-Step Test in Coronary Artery Disease

Henry I. Russek, Staten Island, N. Y.

At present there is no general agreement as to what constitutes normal and abnormal electrocardiographic response to stress. Although Master's criteria have been widely used in the interpretation of the two-step test, many investigators have reported a high incidence of false positive responses by these standards. Recent emphasis has been placed on the amount of S-T depression and the configuration of the S-T segment necessary for an unequivocal diagnosis of coronary insufficiency.

The test was applied to 186 patients known to have either angina pectoris or a healed myocardial infarction. By the criterion of ischemic S-T segment depression alone the test was positive in 81.3 per cent; when Master's other criteria were also imposed, the test was positive in 81.7 per cent. The test was applied further to 108 normal persons. By the criterion of ischemic S-T segment depression alone the test was negative in all; when Master's other criteria were also imposed, the test was positive in 19.4 per cent. While a negative result does not exclude coronary insufficiency, a positive one strengthens the diagnosis of suspected coronary disease. Although the only conclusive evidence of coronary insufficiency is ischemic S-T segment depression, fewer cases escaped detection when all of Master's criteria were utilized. When sound clinical judgement is employed in conjunction with the test, overdiagnosis is infrequent.

Human Atrial Flutter: Evidence for Circus Movement in Right Atrium

David A. Rytand, David L. Bruns, San Francisco, Calif., and Silvio J. Onesti, Jr., New Haven, Conn.

Review of all accessible necropsied instances of cardiac tumor indicates the occurrence of flutter in 7 with right and 1 with left atrial tumor alone, while fibrillation existed 10 and 14 times, respectively.

Secondly, atrial rate was analyzed in 312 patients with flutter but without quinidine or procaine amide. Of 26 with slight to massive right atrial enlargement, the mean flutter cycle duration was 0.262 second (corresponding rate, 229 per min.). In 20 with mitral valve disease, the mean flutter cycle was 0.208 second (rate 288) but none had massive left atrial dilatation, with which fibrillation is the rule. In a control group of 125 patients without appreciable atrial enlargement and with neither complete A-V block nor bundle-branch block, mean cycle length was 0.207 second (rate 290). Of those with enlarged right atria, there was a correlation between degree of enlargement and prolongation of cycle. Dilatation estimated at tenfold accompanied the longest cycles, 0.32 and 0.34 second (rates 187 and 176). In only 5 of the 26 did the rate exceed 250 per minute, and in them enlargement was slight. The difference between the means (0.262 and 0.207 second) exceeds 5 times its standard error.

Finally, exploration by electrodes in 5 patients suggests that (a) the wave travels upward (esophagus) and then downward (anterior chest wall), and (b) the slow rates noted above are not related to slow velocity. These findings favor a returning activation wave in the right atrium in human atrial flutter.

Electrical and Mechanical Asynchronism in the Cardiac Cycle: Study of 100 Ventricular Premature Beats by Simultaneous Right and Left Ventricular Catheterization

Philip Samet, Miami Beach, Leonard Silverman, Miami, William H. Bernstein, Miami Beach, and Robert S. Litwak, Miami, Fla.

Electrical ventricular asynchronism occurs in bundle-branch block, complete heart block with idioventricular rhythm, the Wolff-Parkinson-White syndrome, and in ventricular premature beats. Theoretically, mechanical ventricular asynchronism would be expected under such circumstances, in either the onset of ventricular contraction or the onset of ventricular ejection. The purpose of the present study is to investigate whether such mechanical ventricular asynchronism occurs when left or right ventricular premature beats are produced by endocardial stimulation in the course of combined right and left heart catheterization.

Right ventricular pressure pulses were recorded on Statham P23AA strain gages and left ventricular pressure pulses on P23D or P23G Statham gages. Nineteen studies were performed on 18 patients with rheumatic or congenital heart disease. The normal relationship between the onset of right and left ventricular contraction during atrioventricular conducted beats varied from −.02 to +.03 seconds. At one extreme, right ventricular systole commenced .02 seconds ahead of the left and at the other extreme, left ventricular systole started .03 seconds ahead of the right.

Right and left ventricular pulse pressures were recorded during the course of 100 ventricular premature beats. In 20 of the 24 analyzed right ventricular premature, mechanical asynchronism was absent. In 52 of the 76 analyzed left ventricular premature beats mechanical asynchronism in onset of the contraction was again absent. In summary, therefore, mechanical ventricular asynchronism was not present in 72 out of 100 ventricular premature beats with widened aberrant QRS complexes.

Use of an Inert Radioactive Gas, Kr^{85}, in the Detection and Quantification of Left-to-Right Shunts

Richard J. Sanders and Andrew G. Morrow, Bethesda, Md.

The measurement of right heart and arterial concentrations of an inhaled inert gas has proved a reliable method for the detection of left-to-right circulatory shunts. N_2O was first used for this purpose. More recently, an inert radioactive gas, Kr^{85}, has been employed in a similar manner.

25 Kr^{85} tests were carried out in patients with and without left-to-right shunts. A cardiac catheter was positioned in the pulmonary artery and a needle was inserted into a peripheral artery. The patient then inhaled a mixture of Kr^{85} and air (0.4 mc. per L.) from a spirometer or cylinder. Between the tenth and thirtieth seconds of inhalation blood samples were drawn simultaneously from needle and catheter. The beta emissions of each sample were counted in a continuous gas flow Geiger tube and the radioactivity of the pulmonary arterial sample was expressed as a percentage of the activity in the systemic arterial sample.

In the absence of a left-to-right shunt, the pulmonary arterial sample was always under 15 per cent. In the presence of a shunt, the pulmonary arterial content ranged from 20 per cent, in patients with very small shunts, to over 70 per cent, in patients with large ones. A reliable estimate of the pulmonary systemic flow ratio could be obtained by relating the systemic arteriovenous difference in Kr^{85} content to the pulmonary arteriovenous difference. In all patients, N_2O tests were also carried out and the results of the N_2O and Kr^{85} tests correlated well. In 54 patients, samples for blood O_2 determinations were also obtained. There were 7 diagnostic errors with the O_2 method and none with the Kr^{85} test.

Measurement of the Myocardial Blood Flow in the Closed Chest Rat and the Effect of Drugs and Hemorrhage

Leo A. Sapirstein, Columbus, Ohio

After a single intravenous injection of any indicator foreign to the body it is distributed among the organs initially in proportion to their share of the cardiac output, and ultimately in proportion to their available space for the indicator. In the case of K^{42} and Rb^{86}, the transition from "flow domination" to "volume domination" is so slow as to make the early portion of the transition essentially time independent. This makes it possible to measure the blood flow to an organ in essentially undisturbed conditions whenever the early uptake of either of these indicators by the organ can be measured. This has been done for all the major organs of the body in the rat. The myocardial blood flow in this species is 2.5-3.0 per cent of the cardiac output, representing a perfusion rate of about 3 ml. per Gm. per min. The perfusion value is increased substantially by alcohol, papaverine, and epinephrine, in accordance with expectations. The coronary perfusion rate is maintained very well in rats subjected to hemorrhage despite considerable reduction in blood pressure and cardiac output. Pitressin, contrary to expectations, appears to increase coronary blood flow in the rat; this may be due to either a species difference or a time dependent phenomenon. The principle of the method, its sources of error, and its application to blood flow measurement in certain areas in man will be discussed.

Epidemiology of Group A Beta Hemolytic Streptococci as Related to Acute Rheumatic Fever in Miami, Florida: A Six-Year Study

Milton S. Saslaw and James M. Jablon; with the technical assistance of Madelyn G. Saul and Sallie A. Jenks, Miami, Fla.

The relationship of prevalence of group A beta hemolytic streptococci, average antistreptolysin O titer levels, and school absenteeism to frequency of acute rheumatic fever episodes has been investigated since February 1, 1953, in Miami and Dade County, Fla.

Group A streptococci were recovered from 1,603 of 17,409 throat cultures (9.21 per cent). The rate varied significantly ($p < 0.001$) depending upon the age range of the population sample. Age groups studied were 0-6, 6-9, 9-15, 18-23, and over 23 (adults). Over 11,000 cultures taken from the throats of children 6-9 years old showed that 12.29 per cent were positive for group A organisms; only 2 of 863 cultures (0.23 per cent) taken from mothers of 7 to 8 year old children harbored these organisms. Other age groups fell between these two levels. Serial cultures taken from the same population samples also showed that frequency rates of recovery were related to age.

Average antistreptolysin-O titers revealed comparatively little change with age. Levels of less than 12 units, however, were seen infrequently after childhood.

Data collected by means of case registry, with intensive follow-up, demonstrate that 64 acute rheumatic episodes occurred in Dade County after October 1, 1955. Forty-two met Jones' Criteria. Of the 64 attacks, 19 were in children 6-9 years old, the highest incidence rate in any population age group.

The highest incidence rates of acute rheumatic fever episodes and recovery of group A beta hemolytic streptococci were obtained in the 6-9 year age range.

Experimental Creation of Mitral Insufficiency Without Alteration of Valvular Structure

Victor P. Satinsky, Richard N. Baum, and Eugene V. Kompaniez, Los Angeles, Calif.

In the past, an experimental basis for dealing with mitral insufficiency has been hampered by the need to consider the alterations in anatomy employed to create an incompetent valve. To overcome such objections, and to establish more nearly normal control animals, a "physiology mitral insufficiency" can be created in the experimental animal in the following manner: Employing either a left- or right-sided approach to the mitral valve, a #0,3-0,5 cm. bore polyethylene tube 7-10 cm. in length is passed through the mitral orifice and is fixed both to the apex of the left ventricle and either to the left atrial appendage or left atrium, in accordance with the approach used. The tube is previously treated with aqueous Zephiran, is dried in sterile towels and immersed in desiccol to prevent clotting, and contains multiple perforations which permit ventricular blood to coarse through the tube back into the auricle, thereby escaping the competent valve. The regurgitant effect is immediate. Care must be taken not to utilize tubes with excessively large bores, since acute heart failure may supervene.

The authors are of the opinion that physiologic studies pertaining to mitral insufficiency are best served by control animals with intact mitral valve structures, and that such animals are more suitable for experimental correction of mitral insufficiency than those in which the valve or chordae tendineae have been distorted or destroyed.

Arteriovenous Fistula of the Kidney: Detailed Review and Report of Three Cases

Charles H. Scheifley, Guy W. Daugherty, Laurence F. Greene, and James T. Priestley, Rochester, Minn.

Only 5 reports of renal arteriovenous fistula appeared before 1953. Subsequently, 7 isolated reports brought the total to 12; the 3 we report make 15.

For the first time, the subject is reviewed monographically, thus: (1) classification, (2) incidence, (3) causation, (4) clinical features, (5) diagnostic procedures, (6) pathophysiologic features. Good evidence supports the thesis that in "congenital" cases, an eroding renal arterial aneurysm is etiologic.

Outstanding clinical features were hypertension (to group IV) and myocardial insufficiency; these contrast markedly with features of the usual peripheral arteriovenous fistula. Dramatic relief of heart failure and lowered reserve (in each previous case, where recorded) and hypertension (in 11 of 12 recorded cases) followed corrective surgery (nephrectomy). A loud, diffuse, continuous bruit invariably was present.

Preoperative and postoperative catheterization and indicator-dilution studies, angiograms and aortograms are diagnostic measures emphasized in our 3 cases. Vena caval arterialization, greatly increased cardiac output and markedly shortened dye-recirculation times were found. Excretory urograms were abnormal in 11 of 12 recorded cases.

The mechanism producing hypertension appears related to loss of pressure, decrease in flow and loss of pulsatile character in the renal artery *distal* to the fistula, giving a Goldblatt-kidney type end-result. A vicious cycle of increasing hypertension followed by increasing flow through the shunt makes heart failure inevitable.

Since 10 of the total 15 cases were reported in the past 4 years, indicating that the lesion is commoner than previously supposed, we advise auscultation over the renal areas in patients with cardiac enlargement or failure of unknown causation with hypertension, or when renal tumors are present.

Exaggerated Reactivity to Serotonin in Patients with Rheumatoid Arthritis and Related Diseases

Arthur L. Scherbel and John W. Harrison, Cleveland, Ohio

Alterations in oxidase enzyme systems may cause certain disease manifestations of rheumatoid arthritis. The nonarticular manifestations could result from a central nervous system abnormality characterized by increased amine oxidase activity or decreased neurohormonal activity. The articular and connective tissue manifestations could be caused by an opposite disturbance resulting in increased catecholamine activity.

Thirty-eight patients with rheumatoid arthritis or related diseases and 16 control subjects were given extravascular injections of serotonin and other amines into the intradermal, periarticular, and intra-articular tissues of the hand to observe whether altered reactivity could be demonstrated.

Responses varied with the type of rheumatic disease, the amine injected, and the technic of injection. Patients with active rheumatoid arthritis or systemic lupus erythematosus demonstrated an exaggerated response to serotonin characterized by rapid spread of erythema, swelling, and cyanosis, lasting from 1 to 8 hours. These patients had a less dramatic exaggerated response to the other amines. Control subjects showed only mild localized erythematous swelling without cyanosis.

Thirteen patients were given a serotonin antagonist intravenously at the height of the reaction. Cyanosis disappeared completely in 6 patients given 2-bromo-d-lysergic acid diethylamide and in 1 given hydergine. Definite but incomplete clearing occurred in the remaining patients.

Vasoconstriction and Vasodilatation by Sphincter Muscles in the Capillary Circulation of the Heart

Sidney Scherlis and D. Vincent Provenza, Baltimore Md.

The authors have demonstrated sphincter muscles in the capillary circulation of the heart of man and dog, and have studied the influence of various agents upon the caliber of the smaller vessels of the myocardium in dogs. The sphincter muscles have been demonstrated histologically, and have a nerve supply. Dilatation and constriction of the smaller muscular vessels of the heart have been demonstrated (1) by observing directly the circulation on the surface of the living dog's heart under the dissecting microscope; (2) by recording this photographically; and (3) histologically in deep and superficial vessels after proper fixation of the myocardium. This method shows that alteration in capillary size is associated with relaxation and contraction of sphincter muscles distributed along the precapillaries, metarterioles and arterioles.

Injection of adrenalin, levarterenol and neostigmine retrospectively has been shown by this method to be followed by decreasing caliber of the myocardial capillaries and metarterioles. The constriction which followed administration of adrenalin was reversed by injecting phentolamine methanesulfate (Regitine). Injection of nitroglycerin was followed by dilatation of the smaller vessels of the myocardium.

This demonstration of sphincter muscles, supplied with nerves, supports the concept of coronary vascular spasm, at least with regard to the smaller myocardial vessels. The influence of various drugs and other stimuli upon these sphincter muscles and upon the caliber of the smaller myocardial vessels, shown by direct observation and histologically, emphasizes the importance in the coronary circulation of alteration in the lumens of the smaller myocardial vessels.

Urea Gradient and Active Transport in Renal Tissue During Urea Conservation

Bodil M. Schmidt-Nielsen† and Roberta M. O'Dell, Durham, N. C.

The renal regulatory mechanism for urea excretion has been investigated. Sheep were used because of their marked ability to regulate urea excretion. When a sheep, on a low-protein diet, is conserving urea, the urine urea concentration is about 5 times that of the blood, even at low urine flows. However, during rapidly rising urine flow, the urine urea concentration may increase temporarily as much as 3 times. The finding indicated that some region of the kidney had a higher urea concentration than the urine. Analysis of the renal tissue of sheep on low-protein diet showed that the urea concentration in the outer zone of the medulla was 5 times higher than the urine, while the cortex and tip of papilla had approximately the same concentration as the urine. On the other hand, in animals on normal protein intake the urea concentration increases progressively from cortex toward papilla tip. Studies of the uptake of the urea by kidney slices in vitro showed that, in contrast to an animal on a normal diet in which active uptake can be demonstrated in cortex as well as medulla, the sheep on low-protein diet showed no active uptake by the cortex. The outer zone of the medulla, however, showed sub-

stantial uptake. These findings may be interpreted as an abolishment of the cortical but not of the medullary, urea transport during urea conservation. They are consistent with the counter-current multiplier hypothesis for urea.

Does Alcohol Increase Coronary Blood Flow and Cardiac Work?

Jerry E. Schmitthenner, Joseph H. Hafkenschiel, Ivan Forte, A. Jane Williams, and Cecelia Riegel, Philadelphia, Pa.

Others, in 1955, showed that ethanol blood concentrations 65 to 150 mg. per cent increased coronary flow in anesthetized open-chest dogs. They suggested simultaneous measurements of effects of alcohol on cardiac work, oxygen consumption and coronary blood flow. In 5 pentobarbitalized dogs, 3 having been studied 4 times, we compared changes of 9 paired studies (physiological saline infusions) with 8 observations before and after 30 Gm. ethanol (infused 33 mg. per Kg. per min.) intravenously as to these differences: coronary flow (coronary sinus intubation with nitrous oxide desaturation), cardiac output (direct Fick), left ventricular work and myocardial uptake of pyruvate, lactate, glucose and oxygen.

With arterial ethanol concentrations above 70 mg. per cent (70 to 120), total oxygen uptake, cardiac output and left ventricular work (from 6.7 to 8.1 Kg. meters per minute per 100 Gm.) increased proportionately. Mean arterial pressure and heart rate were unchanged. Coronary sinus venous oxygen content and saturation increased with lesser oxygen extraction. Coronary flow showed no consistent increase in mean values. Left ventricular oxygen consumption was reduced, resulting in apparent improved mechanical efficiency (from 15 to 20 per cent). The only effect on carbohydrate metabolism was decreased arterial pyruvate concentrations.

Alcohol's effect is to dilate peripheral vessels as body oxygen uptake rises. The greater venous return led to increased diastolic filling, stroke volume and stroke work. Alcohol differs from other agents recently tested (nicotine, norepinephrine and epinephrine) in that myocardial oxygen demand was not greater when cardiac work increased. Why work was increased disproportionately with cardiac oxygen consumption was not elucidated.

Automatic Computing Oximeter for Estimation of Cardiac Output

Paul Sekelj and Wanda Jegier, Montreal, Quebec, Canada

Estimation of cardiac output by the dye dilution method with an automatic computing oximeter is described. This instrument provides a quantitative and continuous measurement of the arterial concentration of Evan's blue dye by performing a computation of the data obtained from the ear by means of a photoelectric earpiece. This method has the obvious advantage of doing away with the necessity of collecting and analyzing blood samples for the purpose of calibrating individual dye dilution curves.

Satisfactory agreement is found between the nearly simultaneous estimates based on the direct Fick procedure and on the automatically computed dye concentration values in a group of 14 subjects with various cardiovascular and/or pulmonary anomalies, excluding intracardiac shunts. With the age of the subjects varying from 3 to 55 years, the hematocrit value from 32 to 50 per cent, and the arterial oxygen saturation from 71 to 100 per cent, the cardiac output estimates by the direct Fick procedures are: 3.83 ± 0.42 (0.90–9.84) L. per minute, as compared with 4.01 ± 0.17 (0.57–4.09) L. per minute by this method. The correlation is 0.743 and the S.D.D. is 0.88 L. per minute.

Average values and ranges of cardiac output determinations in 16 normal adults, aged from 24 to 54 years, and in 11 normal children, aged from 5 to 13 years, were: 5.27 ± 1.34 (3.26–8.31) L. per minute, and 3.03 ± 0.55 (2.15–4.11) L. per minute per M.^{2} for the adults and 3.51 ± 0.913 (2.54–5.42) L. per minute and 3.312 ± 0.867 (1.90–4.63) L. per minute per M.^{2} for the children. There is no significant difference ($p < .50$) between the cardiac index values found in adults and in children.

Use of I^{131}-Labeled Fat in the Study of Lipid Handling in Patients with Coronary Artery Disease

Robert H. Seller, Jonas Brachfeld, Herschel Sandberg, and Samuel Bellet, Philadelphia, Pa.

Fasting blood samples for determining serum cholesterol, lipidphosphorous, and lipoprotein electrophoretic patterns were obtained from 51 normotensive males. They were then given a test meal containing 24 Gm. of fat tagged with 100 μc. of I^{131} labeled triolein. Serial blood samples were drawn and assayed for the radioactivity (per cent ingested dose) contained in the whole blood (WB) and the fraction (TCA) precipitable by trichloracetic acid.

The study included 20 "normal" subjects (19-53 years) with no evidence of coronary artery disease by history, physical examination, and electrocardiogram. Their mean values at peak time and 24 hours were: WB^P, 11 per cent; TCA^P, 4.1 per cent; WB^{24}, 2.9 per cent; TCA^{24}, 0.6 per cent. In 21 "abnormal" subjects (27-52 years) with clinical and electrocardiographic evidence of pre

vious myocardial infarction, mean values were: WB^p 19.9 per cent; TCA^p, 10 per cent; WB^{24}, 4.9 per cent; TCA^{24}, 1.6 per cent. Ten patients with "heterogenous" abnormalities (marked obesity, intermittent claudication, etc., precluding their incorporation in the normal group), who displayed no evidence of myocardial infarction were also studied. The differences between the "normal" and "abnormal" means were highly significant statistically ($p < 0.0005$).

A test was considered pathologic when 1 or more of the 4 values (WB^p . . . TCA^{24}) exceeded its corresponding "normal" mean by 2 or more standard deviations. Two "normal" and 7 of the "heterogeneous" subjects showed pathologic lipid handling tests, as did every infarction patient, although many had normal conventional serum lipid parameters.

These results suggest that, besides its clinical value, this test may provide a tool for elucidating an important metabolic disturbance present in patients with coronary artery disease.

Effect of Chlorothiazide on Severe Arterial Hypertension, Including Patients Previously Subjected to Sympathectomy and Adrenalectomy

Alfred M. Sellers, Frans J. Barends, Maurice E. Goldman, M. August Lindauer, and William A. Jeffers, Philadelphia, Pa.

Chlorothiazide was administered orally for an average of 4 months to 70 outpatients whose hypertension had been refractory to prior treatment. Thirty-one patients were in Smithwick group IV; 11 had suffered cerebral vascular accidents; 16 had chronic congestive heart failure; and 14 had blood urea nitrogen ranging from 20 to 37 mg. per cent. Seven patients had failed to respond to either thoracolumbar sympathectomy alone or subdiaphragmatic sympathectomy plus total or subtotal adrenalectomy.

Control blood pressures for all 70 patients averaged 212/123 mm. Hg supine and 206/122 mm. Hg standing. Following addition of chlorothiazide to the prior therapeutic regimen, blood pressures averaged 174/97 mm. Hg supine and 161/98 mm. Hg standing. Twenty-three patients became normotensive; failure to respond (5 patients) correlated best with diminished renal function. Blood pressure fall was greatest when chlorothiazide (500 mg. twice daily) was combined with mecamylamine (2.5 mg. 4 times daily). Chlorothiazide and reserpine (0.25 mg. daily) offered a satisfactory combination for patient acceptability and blood pressure response.

Control blood pressure for the 7 sympathectomy-adrenalectomy patients averaged 220/134 mm. Hg supine and 203/126 mm. Hg standing. After chlorothiazide the average blood pressure was 168/97 mm. Hg supine and 139/87 mm. Hg standing. Symptomatic postural hypotension was common in this group, although chlorothiazide dosage averaged only 500 mg. daily. Adrenal replacement therapy was not altered and electrolyte imbalance did not occur. In these patients, chlorothiazide was effective without the addition of other antihypertensive agents.

Timed Vectorcardiograph as a Measure of Right Ventricular Work

Ronald H. Selvester and Donald E. Griggs, Los Angeles, Calif.

The timed vectorcardiogram (TVCG) as previously reported, combines the main advantage of the spatial vectorcardiogram (SVCG), i.e., graphic portrayal of the vector forces, and the timed relationships of the electrocardiogram (ECG) into a simplified graphic method. Good correlation has been reported with the conventional ECG. The TVCG has been studied in our laboratory in over 600 subjects (with normals and abnormals). Right and/or left heart catheterization has been done in 100 of these, and provides the basis for the present report. These included 66 cases of congenital heart disease, 30 acquired heart disease, and 4 in which no evidence of heart disease was demonstrable.

A scattergram will be presented in which the predicted right ventricular pressures from the TVCG pattern are plotted against the observed right ventricular pressures at cardiac catheterization. This includes 25 interatrial septal defects, 13 pulmonary stenoses, 19 interventricular septal defects, 20 with predominantly mitral stenosis, and 4 with no organic heart disease. Nine cases of patent ductus arteriosus and 10 with significant aortic valve lesions were excluded from this series because they produce predominantly left ventricular work. Good correlation was observed between the predicted and the observed values (mean variation less than 2 mm. of Hg with a mean standard deviation of $\pm$ 8.04).

It would appear that here is a reliable method of evaluating right ventricular overload short of cardiac catheterization. In those situations (particularly postoperative follow-up of septal closures and valvulotomies) where the main measurement needed is the right ventricular pressure, right heart catheterization may be unnecessary.

Timed Vectorcardiogram in Rheumatic Heart Disease

Ronald H. Selvester, Donald E. Griggs, and Paul Smith, Los Angeles, Calif.

The main advantage of the spatial vectorcardiogram (SVCG) is its graphic portrayal of the in-

stantaneous and mean vectors throughout a cardiac cycle. However, time relationships between these forces, such as rate, rhythm, PR and QT intervals, recorded on the standard 12-lead electrocardiogram (ECG) are not shown at all. The timed VCG (TVCG), as previously reported, combines the time and vector relationships into a simplified, graphic method.

In the past year and a half we have studied 77 patients with rheumatic heart disease by this method, all of whom were being considered for valvulotomy. Thirty-one had atrial fibrillation and mitral valve disease. Of the 46 with a normal sinus rhythm, 34 had predominant mitral disease, 8 aortic, and 4 combined.

Of the 46 with normal sinus rhythm, 31 had clear-cut evidence of left auricular enlargement in their timed VCG. Only 17 had ECG criteria of left atrial enlargement, and 30 had x-ray evidence of posterior deviation of the esophagus. Of the total 77 patients studied, the TVCG revealed a balanced tracing without evidence of hypertrophy in 12 cases (31 by ECG); right ventricular hypertrophy in 43 cases (23 by ECG); left ventricular hypertrophy in 22 cases (23 by ECG); of this latter group 16 were combined (6 by ECG).

In summary, the timed VCG revealed the arrythmias and left ventricular hypertrophy as adequately as the ECG in rheumatic heart disease. Further, the TVCG revealed evidence of left atrial hypertrophy, right ventricular hypertrophy, and combined hypertrophy earlier than the conventional 12-lead ECG.

Effect of Cardiac Dilatation upon the Electrocardiographic Pattern of Left Ventricular Hypertrophy

Arthur Selzer, David Y. Naruse, Elihu York, and Kenneth A. Kahn, San Francisco, Calif.

Recent interest in the question as to whether the electrocardiograph is capable of distinguishing between concentric ventricular hypertrophy ("systolic overload") and hypertrophy associated with dilatation ("diastolic overload") prompted this electrocardiographic-pathologic study, organized to compare findings in the 2 types of hypertrophy of the left ventricle. Out of a total of more than 500 cases in which cardiac weight exceeded 500 Gm., a small group of key cases was selected by combined pathologic and clinical evaluation to fulfill rigidly the following criteria: (a) absence of significant coronary artery disease; (b) absence of myocardial fibrosis or infarction; and (c) absence of right ventricular hypertrophy. Of 28 such cases, 12 showed pure concentric hypertrophy and 16 showed hypertrophy with dilatation. The group with concentric hypertrophy showed 10 tracings characteristic of left ventricular hypertrophy, 1 normal record and 1 right bundle branch block. The group with hypertrophy and dilatation showed 9 records with left ventricular hypertrophy, 6 with bundle branch block and 1 with nondiagnostic abnormalities. The only trend detected was the more common occurrence of conduction defects, of widening of the QRS complexes and of left axis shift in hypertrophy with dilatation. In view of the wide overlapping of findings in the 2 groups, it is concluded that in left ventricular hypertrophy the addition of dilatation to the pure increase in ventricular muscle mass does not produce sufficiently characteristic electrocardiographic changes to suggest a distinctive pattern.

Relationships of Hypertension and Experimental Pyelonephritis in the Rat

Alvin P. Shapiro, Pittsburgh, Pa.

Production of chronic pyelonephritis in rats by repeated intracardiac inoculation of bacteria and renal massage as previously described, resulted in pathologic and functional changes in the kidney similar to those in man. Tubular lesions predominated while glomeruli were relatively intact. Functionally, concentrating ability was impaired early while azotemia appeared late. Hypertensive vascular disease, however, was not a significant finding.

Absence of significant hypertension suggested increased susceptibility to renal infection as an alternative explanation for the clinical association between chronic pyelonephritis and hypertension. This possibility was studied as follows: Inoculation of *E. coli without renal massage* produced no gross pyelonephritic lesions in kidneys of 15 normotensive rats, duplicating earlier studies in which the necessity of renal massage for production of *E. coli* pyelonephritis in normal rats was established. Contrariwise, in 16 rats made hypertensive with DCA and salt, inoculation of *E. coli without massage* resulted in gross lesions in 31 per cent (10 kidneys). With massage, gross lesions developed in 54 per cent (14/26) of normotensive and 75 per cent (18/24) of hypertensive kidneys.

The effect of pyelonephritis on pre-existing hypertension is currently under study. In a second series of rats with DCA hypertension, average systolic blood pressure rose from 147 mm. Hg to 161 mm. Hg 1 week after induction of *E. coli* pyelonephritis, but returned to initial level after 3 weeks. Blood pressure did not rise in hypertensive controls.

These data indicate that in rats, hypertensive vascular disease does not result from chronic pyelonephritis alone. Rats with hypertension seem more susceptible to pyelonephritis and this renal infection may temporarily aggravate pre-existing hypertensive disease.

Clinical Differential Diagnosis of Atrial and Ventricular Septal Defects

Morse J. Shapiro and Robert B. Kalmansohn, Los Angeles, Calif.

Since the introduction of catheterization of the heart there has developed a tendency to accept results from this procedure as definitive. We have been misled in several instances by erroneous conclusions drawn from catheterization findings. This had led, in 3 instances, to faulty surgical intervention. It was our impression that a fairly accurate differential diagnosis could be made on the basis of clinical findings. A thorough knowledge of the differences between atrial and ventricular septal defects should aid the clinician in avoiding errors resulting from catheterization studies. Accordingly, we have analyzed approximately 50 cases of septal defects, from the point of view of clinical, roentgenologic, and electrocardiographic findings. Septum primum defects of the atrial septum are excluded from this study. This review has resulted in the following conclusions: 1. Clinical manifestations of these two lesions are distinctive enough to warrant a fairly definitive differential diagnosis. 2. Roentgen findings indicate both right and left heart involvement in ventricular septal defects, while only the right heart is involved in atrial septal defects. 3. Fluoroscopy reveals much more flooding of the lungs in interatrial septal defects than in interventricular septal defects, the size of the heart being equal. 4. In all but one of our cases of ventricular septal defects, the electrocardiogram revealed evidence of both right and left ventricular hypertrophy, while in atrial septal defects, there was no evidence of left ventricular hypertrophy. 5. Patients with erroneous diagnoses resulting from catheterization studies and faulty surgical intervention were studied.

Effects of Infusions of Acetylcholine on Pulmonary Vascular Resistance in Patients with Pulmonary Hypertension and Congenital Heart Disease While Breathing Air and Oxygen

John T. Shepherd, Herbert J. Semler, and H. Frederic Helmholz, Jr., Rochester, Minn.

The object of the present investigation was to determine the role of the vascular smooth muscle in the pulmonary hypertension associated with congenital heart disease. Acetylcholine was administered by constant-rate infusion into the pulmonary arteries of 10 patients having pulmonary hypertension associated with atrial or ventricular septal defects. The dose used did not cause changes in heart rate and systemic pressure, nor affect the respiratory pattern.

The oxygen consumption, oxygen content of pulmonary-artery and radial-artery blood, and pulmonary-artery pressure were recorded continuously before, during, and after the infusion. The degree of any venoarterial shunt was determined by dye dilution curves in order to estimate the oxygen content of pulmonary venous blood. These data were then used to determine changes in pulmonary vascular resistance during the infusion of acetylcholine.

Changes in pulmonary resistance were estimated in each patient while breathing air and while breathing 99.8 per cent oxygen. Eight of 10 patients showed a significant decrease in resistance during the acetylcholine infusion while breathing air, and while breathing oxygen without acetylcholine. Administration of acetylcholine during inhalation of oxygen produced a further drop in resistance.

It is concluded that these changes in resistance are due to an increase in caliber of pulmonary vessels. The results indicate the important role played by smooth-muscle activity in the maintenance of the pulmonary vascular resistance in patients with congenital heart disease.

Studies on the Type-Specific Immune Response to Group A Streptococcal Infections in Children

Alan C. Siegel and Gene H. Stollerman, Chicago, Ill.

The only antibody known to confer immunity against group A streptococcal infection is that which is directed against the type specific M protein antigen of these organisms. Methods for the detection of this antibody are difficult and information about its behavior in childhood infection is scarce.

A large-scale controlled study of group A streptococcal infections in a pediatric outpatient group is now in progress. Ninety-eight children with infections of known serologic type were studied. These included 72 children with type 12, and 26 children with type 3 group A streptococcal infections who were followed for 6 to 18 months from the time of onset of the acute pharyngitis. Serum samples were obtained on the first, twenty-first, thirty-fifth and sixtieth days following the infection and at 6-month intervals thereafter. One group of children were treated initially with 600,000 units of benzathine penicillin intramuscularly and the other treated symptomatically.

Bactericidal tests for the measurement of type specific antibody were performed on all sera. The same sera were also tested by a new method which depends upon the phenomenon of long chain formation of certain strains of group A streptococci when grown in liquid media to which homologous type antisera are added.

Of 48 children with untreated infections due to either type 12 or to type 3 organisms, 60 per cent

developed measurable type specific antibody as compared with 10.5 per cent of the 48 children with penicillin-treated infections.

The most striking difference in the behavior of anti-M antibody compared with other streptococcal antibodies was the long delay in its appearance. It was usually not detected before the sixtieth day, or longer, from the onset of infection. The frequency of development, and the persistence of anti-M antibody was related to the duration of the convalescent carrier state in both treated and untreated groups.

Results indicate that treatment with a penicillin regimen that effectively eradicated the organism resulted in suppression of type specific streptococcal immunity. The percentage of untreated patients who developed measurable antibody to M protein is considerably less than that reported in epidemic streptococcal infections in military recruits.

Cardiovascular Effects of Norepinephrine and Hydrocortisone Hemisuccinate

Harold S. Small, Stanley W. Weitzner, Gabriel G. Nahas, and Charles R. Hatcher, Jr., Washington, D. C.

We have attempted to confirm in the dog the frequently reported observation of the potentiation of the cardiovascular response to norepinephrine by hydrocortisone hemisuccinate. Ten Starling heart-lung preparations were given norepinephrine, either as a single 5 μg. dose or as a 2-minute infusion (5 μg. per minute), while cardiac output and blood pressure were measured. A repeat dose 15 to 20 minutes after administration of 10 mg. of hydrocortisone evoked a quantitatively similar response. Failure to observe potentiation in normal heart-lung preparations led to the use of bilaterally adrenalectomized dogs (maintained until 48 hours prior to testing on cortisone acetate or DOCA in oil), both as blood donor and preparation animal. In 3 such preparations similarly tested, no potentiation was observed. The blood pressure response to norepinephrine was next tested in the intact dog. Two dogs were tested under local anesthesia with single 30 μg. doses, and a third was tested with an infusion (5 μg. per minute) while under light Nembutal anesthesia. Thirteen adrenalectomized dogs (maintained until 24 hours prior to testing only on DOCA in oil) were further tested under various conditions: either awake or anesthetized (ventilated, with either 100 per cent oxygen, or breathing spontaneously); either with a single dose (1 to 30 μg.) or with a constant infusion (30 to 50 μg. per Kg. per hour). The response of all animals to norepinephrine was unchanged after the administration of hydrocortisone. It was further noted that all animals maintained a constant blood pressure response during the 10 to 90 minute period of norepinephrine infusion before administration of hydrocortisone.

Proteins of the Rat Heart: Effect of Growth, Hypertrophy, Starvation and Cortisone Administration

Harry Sobel, Los Angeles, Calif.

Single rat hearts were fractionated by means of extractions with low ionic strength buffers of pH 5.5 and 7.2, high ionic strength phosphate-pyrophosphate buffers, differential centrifugation and electrophoresis, into 13 protein fractions. During growth, various protein fractions accrued in a disproportionate manner. For example, the growth of components designated α- and β-myosin greatly exceeded that of the whole organ. Hypertrophy was produced following daily exposure to 100 F. and 25,000 feet simulated altitude. After 48 hours of accumulated exposure time, heart weights increased nearly 50 per cent. Protein growth during hypertrophy did not parallel normal growth. Greatest increases were observed in β-myosin and the low ionic strength extractable fraction with lowest mobility of pH 7.6. There also appeared to be a large increase in myoglobin. Following starvation to a loss of 40 per cent of body weight, the pattern of protein loss in certain respects was the reverse of that observed in hypertrophy, but in general appeared to be unique. When cortisone was administered to produce a loss of 20 per cent of body protein, only moderate disturbances were observed in the cardiac protein pattern. The concept is proposed that the response of each protein in an organ to a given situation is in general related to the particular functional activity played by that protein and to the current requirements for its services.

Relation of the P-PR Segment Ratio to Atrial Volumes

Louis A. Soloff and Jacob Zatuchni, Philadelphia, Pa.

Although the P wave may be characteristically deformed in mitral stenosis, neither the P wave findings nor the P-R intervals are directly related to the degree of left atrial enlargement. Recently, it has been suggested that the P-PR segment ratio permits recognition of enlargement of either the left atrium, right atrium or both. Because no anatomic evidence was given to support this conclusion and because our experience indicates that angiocardiography may demonstrate left atrial enlargement in diseases thought to affect only the right heart, and right atrial enlargement in diseases thought to affect only the left heart, their hypo he-

sis was tested in 10 subjects with rheumatic heart disease and isolated severe mitral stenosis. The atrial volumes were measured after opacification by simultaneous biplane stereoscopic venous angiocardiography.

The left atrial volumes varied from 209 to 577 ml. and the right atrial volumes from 96 to 269 ml. The P-PR segment ratio varied from 0.5 to 3.0. It was 2.0 or more in 3, less than 1 in 3, 1 in 2, and 1.3 in 1. The remaining 1 had a prolonged duration of the P wave but no detectable P-R segment.

The P-PR segment ratios could not be significantly correlated with the volumes of the left atrium, right atrium or with the ratio of one to the other. Moreover, combined atrial enlargement could not be distinguished from left atrial enlargement alone by the P-PR segment ratio.

For these reasons, we believe that, although the P-PR segment ratio may have clinical value, it has no precise anatomic meaning, either with respect to the volumes of the atria or in their relationship to each other.

Cardiac Chamber Volumes and Their Significance in Rheumatic Heart Disease with Isolated Mitral Stenosis

Louis A. Soloff and Jacob Zatuchni, Philadelphia, Pa.

A study was made of 18 persons with surgically confirmed, isolated severe mitral stenosis to determine volume of each of the cardiac chambers opacified by the technic of simultaneous biplane stereoscopic venous angiocardiography. Volume was measured best by the conventional method and is represented by the product of the area in the frontal plane and the greatest linear diameter perpendicular to it. Total cardiac capacity is the sum of the chamber volumes.

The chamber volumes were as follows: right atrium 96 to 395 ml., right ventricle 63 to 311 ml., left atrium 209 to 582 ml., and left ventricle 41 to 207 ml. The right atrium was larger than the right ventricle in 10 cases and exceeded 200 ml. in 7. Almost always, the left atrium was the largest chamber. The left ventricle was not invariably small and frequently was not the smallest chamber. There was wide variation in the relationship of the chamber volumes to each other.

Total cardiac capacity varied from 595 to 1,3 ml. A significant relationship was demonstrated between the total cardiac capacity and the volume of each chamber except the left ventricle. However, if the total cardiac capacity was less than 1,000 ml., it was significantly correlated only with the left atrial volume ($r = 0.8521$, $p < 0.001$), and if greater than 1,000 ml. only with the left ventricular volume ($r = 0.9581$, $p < 0.05$). Finally, a significant correlation was found between the volume of the right ventricle for values greater than 165 ml. and the pulmonary artery systolic pressure ($r = 0.7771$, $p < 0.01$) or mean pressure ($r = 0.7857$, $p < 0.01$).

Responses of Cardiac Murmurs to Norepinephrine

Louis A. Soloff, Michael F. Wilson, William L. Winters, Jr., and Jacob Zatuchni, Philadelphia, Pa.

Drugs which raise or lower systemic arterial pressure were used in an attempt to determine the clinical significance of cardiac murmurs. This report is based upon the effects of venous infusions of norepinephrine sufficient to raise the systemic arterial diastolic pressure at least 15 mm. Hg.

One free of murmurs remained so during the infusion. Two with innocent systolic murmurs were not altered.

Two of 5 with aortic stenosis developed a decreased intensity and a tendency to lose the characteristic diamond or spindle shape. In 1, a decrease occurred only at the mitral region. In the remaining 2, the murmur increased slightly, but in both instances marked bradycardia occurred and ventricular extrasystoles appeared, occasionally in bigeminus.

Two with pulmonary stenosis developed an increased intensity of their murmurs, which became more obviously diamond- or spindle-shaped.

All 6 with mitral regurgitation developed an increased intensity, either early or late or throughout systole. One not originally pansystolic became so. One also developed an early diastolic murmur at the mitral region.

Of 3 with "pure" mitral stenosis, 1 developed an apical systolic murmur.

All 3 with mitral stenosis and regurgitation developed an increase in the systolic component.

Three with aortic stenosis and regurgitation showed no change.

One with aortic stenosis and mitral stenosis with regurgitation showed no change in the aortic murmur but an increase in the systolic mitral murmur.

It would appear that an infusion of norepinephrine may distinguish between an innocent and organic systolic murmur. Norepinephrine tends to distinguish between aortic stenosis, pulmonary stenosis, and mitral regurgitation. Characteristically, the murmurs of the last 2 increased in intensity and maintained their shape and the murmur of the first diminished in intensity and tended to lose its typical shape. Characteristic changes in aortic stenosis may be nullified by marked bradycardia or extrasystoles, or both. Finally, norepinephrine may unmask mitral regurgitation in those believed to have "pure" aortic or mitral stenosis.

Physiologic Technics in the Detection of Mitral Regurgitation

Leonard S. Sommer, Joan W. Mayer, and Maurice H. Laszlo, Miami, Fla.

The clinical recognition of significant mitral regurgitation vis-a-vis predominant mitral stenosis frequently constitutes a perplexing problem. Physiologic studies, and particularly the demonstration of a significant diastolic pressure gradient at the mitral valve, remain the most objective preoperative criteria, notably if supplemented by physiologic challenges. There are instances, however, in which complicating factors, such as recent systemic embolism, extreme obesity, skeletal deformities of the thorax, pulmonary emphysema, and vascular disease of the extremities make the ideal combined right and left cardiac catheterization more hazardous or impossible. Other objective and simple physiological methods would be of great value under these circumstances.

Our studies have been directed at the evaluation of the response of flow and pressure to tachycardia induced by intravenous atropinization during venous cardiac catheterization. When sustained exercise is not possible, the hemodynamic effects of pharmacologically induced tachycardia have been correlated with varying degrees of mitral stenosis and regurgitation. Our second group of studies have been concerned with the response of the pulmonary capillary pressure tracing, continuously monitored by pulmonary arterial pressure tracings, and of flow, to sustained systemic vasoconstriction induced by the intravenous infusion of a norepinephrine solution. Similar studies of direct left atrial pressure tracings have been evaluated.

Our preliminary results lead us to believe that these methods may yield valuable information in selected instances, from the viewpoint of preoperative consideration, postoperative and reoperative evaluation, and long-term study of the natural history of these rheumatic valvular lesions.

Contrast Visualization of the Central Circulation by Selective Cine-Cardioangiography

F. Mason Sones, Jr., Cleveland, Ohio

Improved demonstration of intracardiac anatomy has been achieved by selective injections of contrast media into the right ventricle, pulmonary artery, left atrium, left ventricle, or aorta in patients with congenital and acquired heart disease. Passage of media through the central circulation has been photographed, with 35 mm. cameras, at rates exceeding 48 frames per second, and are studied as individual frames, or in "slow motion" by projection at 4 to 16 frames per second. Five- and 11-inch image amplifiers have been used to increase the brilliance of the fluoroscopic image, permitting high-speed motion picture photography with the least possible x-ray exposure to patients.

In routine clinical use, multiple serial injections of contrast media have been made in 700 patients ranging in age from 4 days to 58 years. One mortality has been, in part, attributable to the procedure.

Comparative Arm and Thigh Blood Pressures in Patients with Aortic Aneurysm

John A. Spittel, Jr., and Edgar A. Hines, Jr., Rochester, Minn.

A comparative study of arm and thigh blood pressures of patients with aortic aneurysm has not been reported. Blood pressures of the arms and thighs, using the cuff method, were determined in 25 patients with proven abdominal aortic aneurysms without occlusive arterial disease. The systolic pressure of one or both thighs of 17 of the 25 patients with abdominal aortic aneurysm was lower than the systolic pressure in the arms. Blood pressure studies in 26 persons of a similar age group without aortic aneurysm or occlusive arterial disease revealed the systolic pressure of the thigh to be higher than the systolic pressure of the arm in every instance. The range by which the systolic blood pressure of the thigh exceeded that of the arm was 15-115 mm. Hg in the control group. In 5 patients with aortic aneurysm, the difference of the thigh and the arm systolic pressures fell into the "normal" range. In the remaining 3 patients with aortic aneurysm, the systolic blood pressure of the thigh exceeded that of the arm, but by less than 15 mm. Hg. Diastolic pressures were recorded but were less consistent.

Similar blood pressure studies in 6 patients with thoracic aortic aneurysm showed the systolic pressure of the thigh to be lower than that of the arms in 5 patients and higher, although by less than 15 mm. of mercury in 1 patient. The comparison of arm and thigh blood pressures is an aid in the diagnosis of abdominal aortic aneurysm.

Hypocalcemic Electrocardiographic Abnormalities in Patients with Liver Disease

David H. Spodick, Boston, Mass.

Electrocardiograms in 18 patients with liver disorders suggested hypocalcemia because of S-T segment elongation resulting in corrected QT intervals (QT_c) of 0.44 or more. Laboratory studies in 9 of these revealed lack of relation to blood chemical findings, notably serum calcium which was normal in 5, depressed in 2 and slightly elevated in 2 others.

Certain phenomena suggest that liver disease may be associated with altered calcium metabolism: intravenous administration of cholates can

depress serum calcium and cause characteristic S-T elongation. Distortion of serum protein pattern may alter ionization of calcium. Elevation of circulating estrogens has caused calcium binding to shift from the albumin and α-globulin to the β- and γ-globulin fractions.

In 3 consecutive patients with cirrhosis and normal serum calcium, elongated S-T segments were shortened by calcium gluconate (540 mg. Ca^{++} intravenously in 14-20 minutes). In 2 other cirrhotics without QT prolongation, identical experiments caused no appreciable change.

The meaning of these observations is not clear. It is speculated that despite even normal blood levels, liver disease may alter the metabolic availability of calcium in some manner.

Hemodynamic Response of Anemic Subjects to Heavy Treadmill Exercise

Brian J. Sproule, Jere H. Mitchell, and Carleton B. Chapman, Dallas, Texas

The response of 8 anemic subjects to heavy exercise was studied by collecting expired air and analyzing blood samples drawn at rest and during exercise from brachial artery, brachial vein and femoral vein for oxygen content, capacity, pO_2 (polarographic), carbon dioxide content, pH and pCO_2 (calculated).

Oxygen intake was less than in 30 similarly studied normal subjects, although equivalent workloads were achieved. At rest, oxygen transport to body tissues (860.3 cc. per minute) was normal; cardiac index (4.92 L. per minute), central blood volume (1.94 L.) stroke volume (84.3 ml.), and minute ventilation (13.22 L. per minute) were increased. At maximal exercise, cardiac index (12.86 L. per minute), central blood volume (3.106 L.) and stroke volume (125.8 ml.) were normal.

The percentage of oxygen utilized was comparable to normal subjects at rest (43.21 per cent) but increased on exercise (90.12 per cent). AVO_2 difference increased, as in normal subjects, 2.17 times and pO_2 did not change significantly from rest to exercise in either venous or arterial blood although venous oxygen content fell. The A-a O_2 transfer gradient was 32.16 mm. Hg at rest and increased only slightly on exercise.

The change from rest to exercise in arterial (7.41 to 7.31) and venous (7.32 to 7.19) pH was less in anemic than in normal subjects as was the change of $AVCO_2$ difference (6.35 VPC at rest to 17.4 at exercise).

The study indicates that anemic individuals react to heavy exercise qualitatively and quantitatively as do normals, but compensatory mechanisms are significantly modified by decreased oxygen carrying capacity.

Prevalence and Incidence of Coronary and Hypertensive Heart Disease in Strata of the Labor Force of a Chicago Industrial Organization

Jeremiah Stamler,† Howard A. Lindberg, David Berkson, Aaron Shaffer, and Albert Poindexter, with the assistance of Wilda Miller, Mildred Colwell, and Yolanda Hall, Chicago, Ill.

Accumulated medical and sociological records from annual examinations in a Chicago utility corporation were analyzed to accomplish an epidemiologic investigation of the cardiovascular-renal (C-V-R) diseases. The population studied was the male labor force, aged 50-59 on January 1, 1954 (784 men). Over 95 per cent were participants in the periodic program. During the 4 years 1954-7, attrition of this population was negligible due to causes other than death or retirement. Three hundred and forty-one men (45 per cent) were free of diastolic hypertension and all C-V-R diseases throughout. Freedom from disease was significantly greater in the nonobese than in the obese. One hundred and sixty-three men (21 per cent) had high relative weights. Diastolic hypertension was prevalent as the sole positive finding in 68 men (9 per cent); its over-all prevalence was 19 per cent. Two hundred and ninety men (38 per cent) manifested C-V-R diseases. Prevalence and incidence of hypertensive heart disease were significantly lower in the nonobese, and in the foreign-born Irish. Thirty-nine cases (11 fatal) of *de novo* coronary heart disease (CHD) were observed, an incidence of 56/1,000/4 years. Mean serum cholesterol, determined during 1958, was 240 mg. per cent; 16 per cent were under 200 mg. per cent. 22 per cent were 275 mg. per cent or greater. CHD incidence was lowest in the nonobese normotensives (20/1,000/4 years). CHD incidence did not vary markedly in subgroups stratified by occupation, physical activity of work, indoor vs. outdoor work, wage vs. salary income, amount of income, place of residence, amount of education, veteran vs. nonveteran status. Native-born Americans had a significantly higher CHD incidence than foreign-born.

Comparative Effects of Quinidine and Reserpine on the Excitability of the Myocardium of the Turtle

Edward Stein and Morris Kleinfeld, New York, N. Y.

The effects of quinidine and reserpine on the refractory period, diastolic threshold, latency, and conduction time were studied in the heart of the snapping turtle employing a method similar to that described by others.

Strength-interval curves of the auricle and ventricle were plotted during the control period, ½ and 2 hours following the administration of the drug into the aorta. Latency and conduction time

also were determined at these times. Quinidine in dosages of 0.1-0.2 mg. per Kg. body weight prolonged the refractory period, elevated the diastolic threshold and prolonged the latency and conduction time in both auricle and ventricle. These changes were more marked at the two hour than at the one-half hour interval. Reserpine in similar dose range showed no significant changes from the control record. In doses of 0.5-1.0 mg. per Kg. body weight, reserpine produced similar changes in these parameters. When compared to quinidine, reserpine was found to be approximately one-tenth as active.

These results demonstrate that reserpine has a quinidine-like action on the excitability of the turtle heart. This is supported by the observations of others that reserpine can prevent the occurrence of multi-focal ventricular beats induced by the administration of epinephrine in chloroform anesthetized dogs.

Peripheral Pulmonary Arterial Stenosis: Correlation of Clinical, Angiocardiographic, and Cardiac Catheterization Findings in 30 Patients

Aaron M. Stern, Norman S. Talner, and Melvin M. Figley, Ann Arbor, Mich.

Peripheral pulmonary arterial stenosis, constriction of the pulmonary artery distal to the valve and proximal to the arterioles has been diagnosed in 30 acyanotic patients since 1953. The sites of stenosis which have been demonstrated in most instances by both cardiac catheterization and angiocardiography were: (1) in the main pulmonary artery; (2) at the bifurcation; and (3) in the peripheral arteries. Combinations of these sites occurred in the same individual. Ten patients had no associated cardiac defects.

Physical examination in the group with isolated pulmonary arterial stenosis was sufficiently typical to suggest this diagnosis prior to catheterization and angiocardiography. Nine patients with stenosis of the undivided pulmonary artery or its main branches had a harsh systolic murmur in the supracardiac region. Characteristically, this murmur was transmitted to the right and left along the course of the pulmonary arterial branches into the axillae and posteriorly. It was much less well heard over the precordium.

Previous reports have emphasized the importance of a continuous murmur, a finding present in only 1 of our patients having no other structural defect. The stenosis in this patient occurred only in the peripheral arterial branches.

The pulmonary component of the second sound at the left second interspace was frequently accentuated irrespective of the location of the stenosis. This finding in association with the above murmurs strongly suggests peripheral pulmonic stenosis.

The correlation of the characteristics of the murmurs with the pulmonary artery gradients and angiocardiographic localization of the stenotic site has been studied.

Variability and Control of Blood and Plasma Viscosity in Rats

Joseph W. Still and Melvin H. Heiffer, Washington, D. C.

Using a preparation which permits the painless removal of aortic blood from rats, a study of the effect of various stimuli on blood and plasma viscosity has been carried out. Pain, epinephrine and norepinephrine were shown to cause immediate increases in whole blood viscosity. These increases were prevented by Dibenzyline, but not by tetraethylammonium or by adrenal medullectomy. It is concluded that acute changes in blood viscosity are mediated through action of the sympathetic nervous system, reinforced and supported by endogenous adrenalin acting at the sympathetic myoneural junction. The results of several other experiments utilizing other slower-acting stimuli (cold, heat, pregnancy, as well as several hormones) most of which caused changes in viscosity, are also reported.

Pulmonary Hypertension Associated with Atrial Septal Defect

H. J. C. Swan, André David, and Robert O. Brandenburg, Rochester, Minn.

Forty patients (13 males and 27 females) with atrial septal defect and pulmonary artery systolic pressure exceeding 60 mm. Hg were studied in the 3-year period, January 1955 to December 1957. In all but 2 of these patients the pulmonary resistance was abnormally increased and in 16 it exceeded 50 per cent of systemic resistance. In 11 cases the magnitude of the pulmonary blood flow exceeded 5.6 L. per minute per M.^{2} All but 2 of the 31 patients studied while breathing air and while breathing 99.5 per cent oxygen showed a decrease in pulmonary vascular resistance under the latter circumstance which averaged 23 per cent; this result demonstrated the contribution of a vasomotor element to the state of the pulmonary blood vessels. Two patients studied on 3 occasions showed a progressive increase in pulmonary resistance over periods of 7 and 8 years respectively. Of the 21 patients who underwent operation, 9 failed to survive and severe pulmonary vascular changes were demonstrated at necropsy. Three of these 9 patients had chronic heart failure; in 5 of the 6 remaining patients, the pulmonary resistance exceeded 40 per cent of systemic resistance. In the 8 surviving patients who were studied after operation, a significant decrease in pulmonary artery

pressure occurred. In 2 patients, the pulmonary vascular resistance was slightly increased after operation, but for the group it decreased an average of 13 per cent. Hence, the increased pulmonary vascular resistance common in these patients appears to be reversible, at least in part. This may be related to the vasomotor component demonstrated in such patients.

Normal Fetal Heart Rhythm as Recorded by Fetal Electrocardiography

Joseph R. Swartwout, New Orleans, La.*

Recordings have been made of fetal heart activity in 40 normal resting patients, varying from 16 weeks gestational age to term, by means of fetal electrocardiography to establish normal variations in fetal heart rhythm. The minute rate of each cardiac cycle was calculated from the time interval between R waves. The outstanding characteristic seen was irregularity of rhythm. The longest interval of constant rate observed was for 20 beats in 3 cases.

The fetal heart rate can suddenly and markedly decrease as early as 21.5 weeks, and by 26.5 weeks this was seen to occur cyclically. Beginning with considerable irregularity for about 2 minutes, it would increase slowly with less irregularity for another 2 minutes. Then a sudden drop in rate occurred within a period of 1 to 3 beats, followed by a rapid increase and the cycle would repeat.

The beat to beat rate change is greater before 31 weeks and is less from then until term. This may indicate a stage in maturing of the fetal cardiovascular system.

Unusual Cases of Cor Pulmonale

Jan Szatkowski, Chicago, Ill.

Case No. 1: 71-year-old white female, admitted to the hospital with history and signs of chronic cor pulmonale, revealed by progressive cardiac failure, dyspnea, cyanosis, and recurrent hemoptysis. She was an old TB case and x-ray revealed multiple calcifications in the mediastinum and lungs.

Postmortem revealed cor pulmonale, which had an unusual mechanism: calcified lymph nodes of both hilar regions compressed several secondary branches of the pulmonary arteries, reducing their size. This produced ischemia of the lungs and overload of the right ventricle. The calcific masses also caused bronchiectases and compressed pulmonary veins, resulting in passive congestion of the lungs without evidence of left ventricular failure.

Case No. 2: A 50-year-old white female, was hospitalized on 3 different occasions and treated for chronic congestive heart failure. She had recurrent episodes of pneumonia from 1948 till 1957, when she re-entered the hospital in marked congestive heart failure, believed to be caused by rheumatic or congenital heart disease.

Postmortem revealed hypertrophy and dilatation of the right ventricle. Probe patency of pulmonale ovale. Organized thrombosis obliterating the left stem of pulmonary artery, and partially organized thrombosis of branches of the right stem. Pulmonary fibrosis with atrophy of the left lung and right lower lobe. Thrombosis of the veins of the left lung.

Severe Left Axis Deviation in the Presence of Pulmonary Emphysema

Frank J. Talbot and James J. Leonard, Washington, D. C.

Severe left axis deviation has been demonstrated in the older age group in 3 principal conditions. These are peri-infarction block due to anterolateral myocardial infarction, advanced left ventricular hypertrophy and chronic coronary artery disease.

It is the purpose of this report to illustrate a fourth cause of left axis deviation which we have found in 5 male patients with severe obstructive emphysema. Although unusual, it is easily distinguished from the other causes if one is aware of its implications. The pattern referred to is that of severe left axis deviation with the QRS vector at −90°, associated with P pulmonale in leads II, III, and AVF, with low voltage most noticeable in the limb leads. All of the patients which have manifested this electrocardiographic abnormality have been pulmonary cripples.

They have uniformly demonstrated severe obstructive emphysema of the "vanishing lung" type with loss of bronchovascular markings by x-ray, low diaphragms and with small "tear drop"-shaped hearts.

Four explanations have been offered for this paradoxical electrocardiogram in the presence of severe lung disease. The first is that the enlarging right atrium and ventricle produce an unusual degree of anatomic rotation of the heart. A second is that combined ventricular hypertrophy somehow produces this peculiar QRS axis. The third is that the patient has occult coronary artery disease in addition to his severe emphysema.

We concur with others in believing that this verticalization of the QRS axis is related to the marked reduction in electrical conductance of the emphysematous lung.

Acoustical Analysis of Coronary Blood Flow

G. Douglas Talbott and David F. Moyer, Dayton, Ohio

It is established that coronary atheromatous formation modifies the dynamics of blood flow. The

identification of the sounds produced by vortex formation in the coronary blood flow constitutes the basis of this project.

A magnetic microphone with a sensing probe attached to the diaphragm is used to measure these sounds, and a frequency spectrum method utilizing electronic filters is used to identify the characteristics peculiar to plaque formation. These characteristic sounds are of the third order of magnitude or less (−60 d.b.) compared to the normal heart sounds heard through the stethoscope.

The 3 principal phases of this project are graphically presented by oscilloscopic slides of the acoustical analysis. Phase 1 involves cadaverous hearts activated by a double reservoir system pumping saline through normal and atheromatous coronary arteries under normal simulated pressure and flow conditions. Phase 2 represents animal corroboration by rabbits made atheromatous by heated cholesterol, in which the plaques are identified and located by acoustical triangulation. Phase 3 includes preliminary steps in the recordings of clinically normal and atheromatous individuals.

Photographic slides of the acoustical spectrum of each phase are utilized to correlate the above findings so that a technic may be evolved for the acoustical detection and anatomical location of coronary atheromatous plaques.

Angiocardiographic Diagnosis of Aberrant Left Coronary Artery from Pulmonary Artery

Norman S. Talner, Aaron M. Stern, and Melvin M. Figley, Ann Arbor, Mich.

The diagnosis of an aberrant left coronary artery originating from the pulmonary artery in infancy may be confused with a number of conditions formerly included under the general diagnosis of idiopathic hypertrophy of the heart. Although the presence of an electrocardiographic infarction pattern is highly suggestive of this lesion, the same pattern has been seen in other conditions at this age. The accurate diagnosis of the anomalous left coronary artery is important because it is the one condition for which there is hope of corrective surgery. Furthermore if the surgical transplantation of the aberrant coronary artery into the aorta is to be of maximal benefit, it would be desirable for the operation to be undertaken before myocardial infarction had occurred.

Through the use of angiocardiography, it has been possible to demonstrate the origin of the left coronary artery from the pulmonary artery. The flow of contrast from the pulmonary artery into the coronary artery is in conflict with the previously accepted concept that the low pulmonary artery pressure prevents perfusion of the myocardium by way of the aberrant vessel. It is further in conflict with the recently suggested aorticopulmonary shunt by way of this anomalously connected left coronary artery through intercoronary communications.

Improved Technics for the Arteriographic Study of Patients with Coronary Sclerosis

Alan P. Thal,† L. Stephen Richards, Richard H. Greenspan, and Murray J. Murray, Minneapolis, Minn.

In a previous report, the feasibility of using arteriographic technics for the study of coronary sclerosis was demonstrated. The development of phasic injection of contrast material has so improved coronary arteriography that it is now regularly possible to study the detailed collateral response to coronary occlusion with a minimum of discomfort to the patient.

A compressed nitrogen driven injector triggered by an electronic control system allows the rapid delivery of radio-opaque medium at any point in the cardiac cycle. This is accomplished by amplifying and suitably delaying the R wave of the electrocardiogram. The injection is made through a side opening catheter placed through the brachial artery to lie about 3 cm. above the aortic cusps. Systolic phase injection has consistently given better coronary opacification. Films are taken biplane at a speed of 6 per second.

Our experience in studying over 45 patients will be presented. Included in this group will be examples of single and multiple coronary occlusions. All patients with angina on effort had occlusion of at least 1 major artery with a marked collateral response. In patients with angina at rest the arterial disease was more extensive and the collateral response less evident. Further arteriographic signs of severe disease are: intimal irregularity, rigidity during systole and diastole, tortuosity and stasis of opaque material.

Effect of Exercise on the Left-to-Right Shunt in Ventricular Septal Defects without Pulmonary Hypertension

E. O. Theilen, J. M. Fisher, R. Sasaki, and W. R. Wilson, Iowa City, Iowa

Systemic and pulmonary blood flows were determined in 7 patients who had uncomplicated ventricular septal defects without pulmonary hypertension. These patients from 15 to 33 years of age were asymptomatic and had good exercise tolerance. Blood samples were obtained from the pulmonary artery, the right atrium, and a brachial artery during the collection of expired air; cardiac outputs were calculated using the Fick principle. Measurements were made at rest and during exercise in the supine position. Arterial oxygen saturation was normal in all of these patients, and evidence of right-to-left shunts was not found. Pul-

monary artery mean pressure increased slightly with exercise, but not more than would be expected in normal subjects. Pulmonary blood flow increased with exercise in 6 of 7 patients but the calculated volume of the left-to-right shunt either remained unchanged or decreased. The volume of the left-to-right shunt expressed as per cent of total pulmonary blood flow showed similar trends.

The data suggest that even in the absence of high pulmonary vascular resistance, exercise does not tend to increase the relative magnitude of the left-to-right shunt, which may actually decrease. We feel that the systemic peripheral resistance and the changing relationships between pulmonary and systemic vascular resistance are important determinants in the control of the shunts in these patients.

Analysis of Clinical Results from the Surgical Creation of Pulmonary Stenosis in 35 Patients with Large Intracardiac Communications

W. Maddux Thompson, Jr., William H. Muller, Jr., and J. Francis Dammann, Jr., Charlottesville, Va.

In view of the generally high mortality rate associated with the open repair of intracardiac defects in infants, a palliative procedure to allow definitive surgical repair at a later and more opportune date would be of interest. Such a palliative procedure must be accomplished at less risk, and not interfere with subsequent corrective surgery. The surgical creation of pulmonary stenosis fills these requirements and achieves the following results: (1) the 2 circulations are brought into better balance; (2) cardiac work load is significantly reduced and decompensation is corrected; (3) stress of high pulmonay blood flow and/or pulmonary hypertension is relieved with consequent prevention of progressive and possibly irreversible pulmonary vascular disease; (4) when pulmonary vascular disease is already in progress, regression may occur.

During the last 8 years, pulmonary stenosis has been created in 35 patients. Extensive pre- and postoperative studies were carried out in addition to pressure determinations at the time of surgery. The data obtained have delineated the degree of stenosis necessary to achieve optimal results. This knowledge, in conjunction with improved selection of cases and surgical experience has resulted in a reduction in mortality rate from 47 per cent in the first 5 years to 27 per cent during the last 3 years. Our results in this group of patients suggest that the procedure might be applied to certain older patients with defects associated with marked pulmonary hypertension and normal or elevated pulmonary blood flow who are not, at the present time, considered operable.

Nature of Idiopathic Heart Failure in Young Negro Males

William J. Tolleson, Joseph M. Merrill, and Richard France, Nashville, Tenn.

A syndrome of severe heart failure occurring in 12 young negro males (average age 31 years S.D. ± 1.5) has been studied. Four of these patients have had postmortem examinations. Eight are living and have had right-heart catheterizations. The clinical features are exertional and nocturnal dyspnea with dilated heart, gallop rhythm and peripheral edema. An apical systolic murmur, narrow arterial pulse pressure and paradoxical pulse are common. Electrocardiograms show abnormal P waves, low voltage in the frontal plane and evidence of left ventricular hypertrophy in the precordial leads. Roentgenograms indicate enormously dilated hearts with diminished pulsations noted at fluoroscopy. Pathologic features are massive cardiac dilatation and hypertrophy (average heart weight 580 Gm. S.D. ± 72) with varying amounts of patchy myocardial necrosis and fibrosis with endocardial thickening and mural thrombi.

Variants of this disease have been described among the natives of East and South Africa and in this country. The hemodynamic abnormalities present in this condition are the subject of this report. The average results of studies performed in 8 patients follow: cardiac index 2.5 L. per minute per $M.^2$ (S.D. ± 0.02); stroke index 29 ml. per minute per $M.^2$ (S.D. ± 2.4); A-V O_2 diff. vol. per cent 5.8 (S.D. ± 1.6); arterial O_2 saturation 95 (S.D. ± 2.0); pulmonary artery mean pressure 29 mm. Hg (S.D. ± 13). Refractory heart failure in some patients caused considerable variation in the total pulmonary resistance (average 534 dynes seconds $cm.^{-5}$ S.D. ± 361) and in the pulmonary vascular resistance (range 68-464 dynes seconds $cm.^{-5}$).

It is concluded that the characteristics of this type of heart disease are biventricular failure, pulmonary hypertension and low cardiac output. When the failure is reversible, normal cardiac dynamics are restored.

General and Coronary Hemodynamic Effects of a Sympathomimetic Amine, Cinnamyl Vonedrine

Elmerice Traks, Donald B. Hackel, and Salvatore M. Sancetta, Cleveland, Ohio

Cinnamyl vonedrine (N-methyl-N-cinnamyl-2-phenylpropylamine hydrochloride), a synthetic substance chemically related to the sympathomimetic amines of the ephedrine series, has been shown to increase coronary flow in anesthetized dogs with little change in blood pressure and heart rate. Its hemodynamic effects have been tested in 14 human subjects following intravenous

administration in a dosage of 0.5 mg. per Kg. body weight. Cardiac output determinations were done in 6 patients (Fick) and coronary flow determinations in 8 patients (nitrous oxide technic).

Heart rate, brachial and pulmonary artery pressure, total oxygen consumption and arteriovenous oxygen differences did not change significantly. Because of directional rises and falls in oxygen consumption and arteriovenous differences, however, there was a significant increase in the cardiac output.

Coronary blood flow increased significantly with no change in coronary sinus blood oxygen content, and with a significant decrease in coronary vascular resistance. As a result, there was a significant increase in myocardial oxygen consumption. The drug seems to have hemodynamic effects in many ways similar to those of aminophylline and may have the same potential of clinical usefulness.

Six-Year Average Follow-up of 460 Consecutive Cardiac Patients

David J. Turell and Herman K. Hellerstein, Cleveland, Ohio

A follow-up study was made of 433 (94.2 per cent) of the first 460 consecutive patients in a clinic.

The follow-up averaged 6 years for the 261 survivors. The remainder died an average of 2.7 years after the initial visit. The highest death rate occurred in patients with hypertensive and arteriosclerotic heart disease, or other combinations: 53.7 per cent (51/95) and 53.8 per cent (7/13) respectively.

The initial functional and therapeutic classification correlated with subsequent mortality: 13.3 per cent (15/125) IA-C, 25.8 per cent (24/93) IIB, 42.3 per cent (41/97) IIC, 50.0 per cent (44/88) IIIC, and 64.3 per cent (18/28) IIID or worse.

Of 248 survivors re-evaluated at the clinic, cardiac status remained unchanged in 42.7 per cent (106), improved in 23.4 per cent (58), particularly in IIB, 11C, and IIIC groups, and became worse in 33.9 per cent (84).

Initially 41.1 per cent (178/433) were employed. At follow-up, the employment status of the survivors improved, increasing to 70.9 per cent (185/261). Of those working, an average of 3.8 days per 100 days employment were lost due to heart disease; 60.9 per cent (81/133) of the group initially unemployed became employed, while only 18.8 per cent (24/128) of the initially employed group became unemployed; 86.6 per cent (375/433) worked at some time during the follow-up period. Only 1 patient died on the job. In no case was it claimed or demonstrated that proper employment was harmful.

Electrophysiologic Studies of Left Ventricular Hypertrophy in Rats

Herman N. Uhley, San Francisco, Calif.

Although left ventricular hypertrophy (LVH) is characterized by increased voltage in the electrocardiogram, the single cell potential in hypertrophy is unknown. This was investigated by inducing LVH in uninephrectomized rats made hypertensive by figure-8 ligature about the remaining kidney. Experimental and control rats were studied 5 to 8 months postoperatively. Under Nembutal anesthesia, vectorcardiograms (VCG-cube system) and its scalar components (bipolar leads) were obtained. Then, with respiration maintained by an intratracheal respirator, the chest was opened and cardiac surface (unipolar) and transmembrane action potentials were recorded with a glass microelectrode from 12 areas of the exposed myocardium.

As expected, 9 of 10 such operated rats had greater heart weights than controls of comparable body weight. Hypertensive rats exhibited increased amplitudes of the mean QRS vector (R wave of bipolar superior-inferior axis greater than in control groups ($p = .01$) and terminal QRS vectors were to the right in 9 of 10 hypertensive rats compared to 2 of 10 controls. Surface potentials as reflected in the sum of R+S waves were not significantly different. However, R waves in leads near the apex were smaller in the experimental than control rats ($p = .01$). Despite the observed VCG and bipolar differences, transmembrane action potentials were comparable (average 91 mv.) in the 2 groups (343 micropunctures).

These data suggest that increased voltages found in ECG with LVH patterns are not the result of changes in single cell generator amplitudes, but are probably due largely to unopposed voltages arising from the thickened left ventricle.

Observations Concerning the Role of Pulmonary Lymph Flow in the Pathogenesis of Pulmonary Edema

Herman N. Uhley, Sanford E. Leeds, John J. Sampson, and Meyer Friedman, San Francisco, Calif.

Previous studies of pulmonary lymphatic drainage were limited by cannulation problems involving the tiny multichanneled right lymph ducts. A technic has been devised in which a chamber is created within the right external jugular vein which traps lymph between the outside of a tube secured in the vein and the wall of the vein. A polyethylene catheter removes lymph from the chamber.

The average right duct lymph flow was 4.2 ml. per hour in 10 normal dogs, but in 4 dogs in which there was presumptive shunting of thoracic duct

fluid the average flow was 18.0 ml. per hour.

In 10 dogs, elevation of pulmonary venous pressure to 30 mm. Hg by introduction of a balloon into the left atrium, resulted in initial increases of thoracic duct flow (approximately 15 min.) and in right lymph flow (approximately 15 min. later). After maintenance of elevated pulmonary venous pressure and progressive increase of lymphatic flow for ½ hour (approximately), critical pulmonary edema ensued. The protein and glutamic-oxaloacetic transaminase, but not the glutamic-pyruvic transaminase content of the right duct lymph increased and decreased with gross elevations and depressions of the lymph flow.

The accumulation of intrapulmonary fluid following elevated pulmonary venous pressure is indicated by increase of pulmonary lymph flow. Hypothetically, when the quantity exceeds the capacity for lymph drainage, critical pulmonary edema becomes apparent. Both increased lymph flow and pulmonary edema are generally promptly decreased with relief of high pulmonary venous pressure.

Occult Renal Impairment in Hypertension

Allan M. Unger, Joseph H. Magee, and David W. Richardson, Richmond, Va.

Clinical tests sufficiently sensitive to detect diffuse renal disease frequently are normal until late in hypertensive disease. To evaluate better the effect of hypertension on the kidneys, inulin-PAH clearances have been determined and these clearances have been compared with the blood urea nitrogen, PSP excretion, 24-hour protein excretion, and the urinary sediment. Seventy-two patients with an average diastolic pressure between 90 and 151 mm. Hg (average 105 mm. Hg) have been studied.

Fifty-three (74 per cent) of these patients had less than ¾ normal inulin clearance and 64 (89 per cent) have less than ¾ normal PAH clearance. Filtration fraction was greater than 0.19 in all except 1, filtration fraction averaging 0.25.

The BUN level was greater than 20 mg. per cent in only 11 of 71 patients. Protein excretion was less than 1 Gm. per 24 hours in 40 of 46 and marked abnormality of urinary sediment was unusual. Proteinuria on abnormal sediment suggested the presence of a necrotizing renal arteriolitis or concomitant primary renal disease.

Although rough correlations exist between inulin-PAH clearances and level of BUN or PSP excretion, considerable overlap is present at both high and low clearance values. In general, great reduction in inulin and PAH clearance correlated well with severe blood pressure elevation or marked cardiomegaly.

The demonstration of marked decrease in inulin and PAH clearances in most of these hypertensive patients emphasizes again the critical effect of hypertension on the kidney, even though other tests of renal function are not abnormal.

Cardiac Ventriculography in the Study of Acquired and Congenital Heart Disease

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Cardiac ventriculography involves the direct needle puncture opacification of the ventricular chambers via a subxiphoid approach. The test is performed under manometric control with electrocardiographic monitoring. Films are taken serially at rapid intervals following instillation of dye into the ventricular chamber.

The present report reviews all our clinical experience with the technic in a large series of patients with acquired and congenital heart disease. The method has been most helpful in the assessment of regurgitation at the mitral and tricuspid valves. Injection of contrast material into the ventricles leads to immediate reflux opacification of the the atria in the presence of dynamic regurgitation. This does not occur with normal heart valves or with stenotic lesions.

The method has been used chiefly to quantitate mitral regurgitation in the presence of aortic stenosis or associated mitral stenosis, as well as certain congenital defects of the atrial septum. It has been employed also to identify traumatic mitral regurgitation following commissurotomy and to evaluate surgical procedures for correction of mitral regurgitation. Ventricular aneurysms are better opacified by this approach than by the conventional angiocardiography.

The major complications of cardiac ventriculography include conduction defects and arrhythmias. Intramyocardial injection of dye is rare. Two hospital deaths followed a period of severe hypotension, but no serious morbidity and no mortalities have occurred in the last 150 patients studied.

Studies on the Pathogenesis of the Aschoff Body

Bernard M. Wagner, Philadelphia, Pa.

Until recently, studies concerning the development of the Aschoff body have been restricted to autopsy material. Biopsies of left auricular appendages during surgery for rheumatic mitral valvular disease present a new source of tissue. Since 1952, a total of 638 biopsies have been examined microscopically. Aschoff's bodies in various stages of evolution were noted in 124 of these; 11 fulfilled the classic histopathologic criteria for acute rheumatic carditis. Histochemical and immunochemi-

cal observations have revealed the following: the earliest recognizable morphologic alteration appears to be a focal degeneration of collagen fibers. This focus becomes metachromatic and may appear as fibrinoid. Sulfated acid mucopolysaccharides, reactive sulfhydryl and α-amino groups, γ-globulin and fibrin are present in this area. Mono- and multinuclear Aschoff cells are positive for acid phosphatase and nonspecific esterase. By these methods, fibrinoid of rheumatic carditis may be differentiated from fibrinoid occurring in other systemic connective tissue diseases. The reactivity of the Aschoff cells suggest they are of mesenchymal origin related to histiocytes. However, the possibility that these cells represent altered fibroblasts cannot be excluded. Attempts to localize streptococcal products by fluorescein-labeled antibody methods have been unsuccessful.

Altered Vascular Responsiveness Following Chlorothiazide or Mercurial Diuresis in Normotensive Subjects

Annemarie Wanko and Edward D. Freis, Washington, D. C.

Although chlorothiazide does not reduce blood pressure in *normotensive* individuals, it may alter their responsiveness to pressor and depressor stimuli. Intravenous infusions of levarterenol, 2 μg. per ml., and trimethaphan (Arfonad), 0.1 per cent, were administered alternately both before and after 3 days of treatment with 1.5 Gm. of chlorothiazide daily.

In 7 normotensive, nonedematous subjects, the blood pressure rise following levarterenol averaged 35 $\pm$ 14 per cent above basal in the control and 20 $\pm$ 8 per cent after chlorothiazide. Trimethaphan reduced the blood pressure 21 $\pm$ 8 per cent before and 29 $\pm$ 15 per cent after chlorothiazide. Thus, chlorothiazide decreased the pressor response to levarterenol and increased the depressor response to trimethaphan. Basal blood pressure was unchanged after chlorothiazide. In the first 24 hours following chlorothiazide, average urine volume increased from 1,970 to 2,530 ml. and mean sodium excretion from 106 to 209 mEq.

Two additional normotensive subjects were tested similarly before and after NH_4Cl plus meralluride. Elevation of blood pressure following levarterenol averaged 34 per cent in the control and 26 per cent following diuresis. Reduction of pressure after trimethaphan averaged 19 per cent before and 37 per cent following diuresis.

After chlorothiazide, venous congestion of the extremities increased the depressor action of trimethaphan, whereas infusion of 500 mg. of 6 per cent dextran restored the blood pressure responses following both levarterenol and trimethaphan to approximate prechlorothiazide levels. These observations suggest that the change in vascular responsiveness following saluretic agents is secondary to the plasma volume depletion previously demonstrated in this laboratory.

Open Heart Surgery for Congenital Heart Disease

Herbert E. Warden, Richard A. DeWall, Richard L. Varco, and C. Walton Lillehei, Minneapolis, Minn.*

More than 475 patients with intracardiac abnormalities have undergone prolonged periods of total cardiopulmonary bypass at normothermic temperatures. During the bypass they were supported by an arterial perfusion of oxygenated blood from an extracorporeal source; their hearts were opened and under direct vision the anatomic correction of these lesions, which heretofore were unamenable to treatment, was leisurely carried out. These operations have been done for a variety of intracardiac malformations of both acquired and congenital origin. The latter have been the most frequent type encountered and will receive the attention at this communication.

The common congenital intracardiac defects in this series have been the isolated interventricular septal defect, tetralogy of Fallot, interatrial septal defect, and atrioventricularis communis. In these lesions, as in the other less common congenital cardiac anomalies which have occurred in this series, the surgical approach has been designed to correct the existing intracardiac pathologic anatomy in such a way as to establish normal intracardiac hemodynamics.

An Analysis of the Circulation as a Self-Regulating System Using an Analog Computer

Homer R. Warner, Salt Lake City, Utah

The circulatory system consists of 2 distensible vascular beds separated from each other by two variable-flow pumps, the right and left ventricles. Sixteen integro-differential equations have been derived to represent the relationship among flow, volume, pressure and time in the various system components. Since this system is a "closed loop," variation in any one of its parameters cannot be accomplished without affecting all the variables. Thus, a valid analysis of performance of the intact circulation can be obtained only by simultaneous solution of all the equations of the system. In this study these equations are solved simultaneously using an analog computer and the computer solutions compared with the time-course of the corresponding physiologic variables previously recorded on a multichannel magnetic tape loop from a human subject or an experimental animal. The theoretical and experimental curves are made to

correspond by varying potentiometers whose setting represent in the computer the coefficients of the equations. Solution of these equations using many combinations of coefficients has allowed a thorough analysis of each parameter's role in determining system performance. Such solutions obtained with a wide range of constant coefficients predict that in the absence of reflex activity the circulatory system will be absolutely stable and will respond rapidly and without overshoot (except at high flows) to transient disturbances such as a Valsalva maneuver. Confirmation of this and other predictions in dogs has been obtained.

Subminiature Intracardiac Manometer

Allan Warnick, Dearborn, Mich., Ellet H. Drake, Herman Alvarez, Jr., C. M. Savage, and John Bell, Detroit, Mich.

Conventional cardiac pressure recording involves the transmission of phasic variations through a fluid column within a catheter and conversion from mechanical to electrical energy at some distance from the site of actual pressure variation. This method has long been known to be theoretically inefficient and to present a probable source of distortion in the finished records.

The new instrument is a subminiature manometer adapted to the leading end of a no. 6 catheter. The pressure sensing element utilizes the strain gage principle and is of hollow construction to permit blood sampling at the site of pressure measurement and in situ calibration by an external manometer. The transducer has a maximum diameter of 2.25 mm., an effective inside diameter of 1.0 mm. and an over-all length of 16 mm. The natural frequency of the transducer is 2,000 c.p.s. when measured in a fluid environment. The transducer is used with a low-level dc transistor preamplifier to provide signals of 4 mv. per mm. Hg. The pressure range of the system is −20 to +300 mm. Hg and the linearity and hysteresis together are better than 2 per cent of range.

Prior to human usage, the instrument was thoroughly tried on dogs whose hearts were subsequently examined for pathology. The catheter presented no problem in manipulation, responsiveness being enhanced by the lead wires in the wall.

Simultaneous recordings from a conventional transducer system and the intracardiac manometer were made by utilizing the hollow structure of the new transducer. A time lag and variations in the form of various wave complexes in the conventional record are noted.

Further clinical work and adaptation for sound recording is in progress.

Central Blood Volume as a Factor in the Regulation of the Circulation

James V. Warren and Arnold M. Weissler, Durham, N. C.

Previous observations have suggested that the amount of blood immediately available to the heart (the central or pulmonary blood volume) may play a role in the regulation of cardiac output.

To evaluate this suggestion, 35 supine and 41 upright subjects were studied, measuring cardiac output, stroke volume, and "pulmonary blood volume" by both dye dilution determinations and a radioactive tracer method. By both methods of study it was demonstrated that the mean "central blood volume" was significantly 17-28 per cent lower in the erect subject than in the supine individual. At this time a high degree of correlation between central blood volume and stroke volume could be demonstrated ($r = .79$), whereas in the supine subjects a much lower degree of correlation was detected ($r = .42$). Cardiac output was similarly correlated, but heart rate did not appear to follow such a relationship. In a group of supine subjects, hyperactive circulatory states were induced by drugs. In these subjects, even in the horizontal position, stroke volume and central blood volume correlated to a considerably higher degree than in the resting supine group and approached the value in the upright subjects.

These observations give evidence of the permissive role that the central blood volume plays in determining stroke volume and cardiac output. When the ratio of stroke volume to central reservoir volume is reduced by either the upright posture or increased cardiac output, than a greater dependence of the stroke volume on the available central pool can be clearly demonstrated, much as in the classic heart-lung experiments of Starling.

Early Metabolic Alterations and Fine Structure Changes in Myocardial Fibers Irreversibly Injured by Ischemia

William B. Wartman, Robert B. Jennings, John P. Kaltenbach, Hisako O. Yokoyama, and Gunther F. Bahr, Chicago, Ill.

A variety of methods—histochemical, chemical and phase, light, electron and x-ray microscopy—were used to study the metabolism of myocardial fibers in an experimental infaret of the posterior papillary muscle of the left ventricle of the dog. Because the site of this infaret is predictable and the necrosis uniform, the earliest stages of infarction may be studied. Under these conditions at least 3 cellular functions are altered.

1. In the first half hour after the onset of ischemia, intracellular glycogen decreases and by 24 hours falls to about 100 mg. per cent, indicating

histochemically the intracellular shift from aerobic to anaerobic metabolism.

2. During the next few hours the cell becomes unable to retain, concentrate or exclude electrolytes, ions and enzymes. Potassium and phosphate leave the cell and within 8 to 13 hours intracellular and extracellular levels become equal. Transaminase begins to leave the cell in 40 to 60 minutes, lactic dehydrogenase in 120, and succinic dehydrogenase in 5 hours. Intracellular water, sodium and chloride increase rapidly.

3. The ischemic cell loses the ability to clear itself of metabolic products such as fat, calcium, and iron which accumulate in the cytoplasm.

Electron and x-ray microscopy show corresponding changes in submicroscopic cytology. Within 5 minutes, mitochondria may become edematous (reversible) or later lose their membranes (irreversible). Within the first half hour, myofibrils relax and capillary walls disintegrate.

Electrocardiographic Pentalogy of Pulmonary Emphysema

Richard H. Wasserburger, John H. Juhl, Howard K. Rasmussen, and Joseph R. Kelly, Madison, Wis.

In previous investigation, it was noted that exaggerated T-a waves were identified in leads 2, 3, AV_F of adults with advanced pulmonary emphysema. Correlation with cardiac rate revealed that T-a wave inscription greater than 1 mm. and a heart rate of less than 100 per minute suggested an emphysematous state. An increased mean P-wave amplitude was also found in the emphysematous group as compared to a control series.

In further attempt to define the electrocardiogram in advanced pulmonary emphysema, 190 patients with severe pulmonary emphysema as determined by detailed pulmonary function testing have been evaluated. From this group, approximately 60 per cent exhibited an electrocardiographic pattern which was so consistent that the probability of existing pulmonary emphysema could be entertained from the electrocardiographic interpretation alone.

These criteria have been called "the electrocardiographic pentalogy of pulmonary emphysema" and consist of the following:

1. Vertical cardiac position.
2. Tendency to low voltage in the standard and augmented limb leads, as well as in the left precordial leads, i.e., V5 through V7.
3. Advanced degrees of clockwise rotation.
4. Prominent P-waves in leads 2, 3, AV_F.
5. Exaggerated T-a waves, greater than 1 mm. in leads 2, 3, AV_F, with a heart rate of 100 per minute or less.

In general, the electrocardiographic changes are felt to be positional in nature, although the factor of incipient right auricular enlargement has not been fully evaluated.

Direct Epicardial Potentials in Right Ventricular Hypertrophy

Richard H. Wasserburger, William P. Young, Karl Siebecker, Jr., and D. Joseph Freeman, Madison, Wis.

Based upon previous electrocardiographic analysis of 400 cases of congenital heart disease established by means of cardiac catheterization, it was observed that the most common electrocardiographic expression of right ventricular preponderance consisted of an rR′ pattern in the right precordial leads which was subtended to 3 variable points, AV_R, $V4_R$ and V_E.

In an attempt to define further the origin and significance of the various right precordial QRS complex patterns in established instances of right ventricular preponderance, direct right and left ventricular epicardial potentials have been recorded from predetermined areas on 12 patients with isolated valvular pulmonic stenosis and tetralogy of Fallot. With but a single exception, a distinct rR′ pattern has been identified as arising from the anteromedial base of the high outflow tract of the right ventricle. Most interestingly, as one approaches the apex of the right ventricle with the exploring electrode, an rS pattern is identified similar to that seen in augmented limb lead AV_L. Also, the timing of the peak of the R′ wave of the right ventricular leads occurs later than the peak of the R wave recorded over the left ventricular surface. This refutes the premise that the tall R′ waves seen in the conventional right precordial leads stem from a posteriorly displaced left ventricle.

The general concept of right ventricular preponderance in infants, children and adults will be reviewed, and clinical variations of this pattern will be shown.

Effect of Molar Sodium Lactate in Quinidine and Procaine Amide Intoxication

Fred Wasserman, Leonard Brodsky, John H. Kathe, Morris M. Dick, and Paul L. Rodensky, Coral Gables, Fla.

Quinidine and procaine amide are widely used in the treatment of various arrhythmias. Unfortunately, there is no method of treatment available for either quinidine or procaine amide intoxication other than discontinuing the agents.

Molar sodium lactate will narrow abnormally widened QRS complexes due to a variety of causes and will rapidly reverse the cardiotoxic effects of hyperkalemia. It has been suggested that the cardiotoxic manifestations of quinidine are similar to those seen with hyperkalemia.

We have shown in the experimental animal that molar sodium lactate will reverse the cardiotoxic effects of both quinidine and procaine amide. In combination with vasopressors, sodium lactate appears to reverse heretofore irreversible experimental procaine amide intoxication. In severe experimental quinidine intoxication (i.e., A-V dissociation), however, molar sodium lactate alone and in combination with vasopressors affords only evanescent improvement in the electrocardiogram which ultimately progresses to death.

This experimental observation of irreversible quinidine cardiotoxicity does not appear to be true in patients. Three patients with severe quinidine and procaine amide intoxication were studied. Toxic manifestations included markedly widened QRS complexes, arrhythmias, hypotension, increased plasma quinidine levels (2 patients), and essentially normal serum electrolytes and chemistries. In these patients, molar sodium lactate alone and in combination with intravenous vasopressors afforded dramatic clinical and electrocardiographic improvement.

These findings suggest that a decrease in the acidosis uniformly resulting from the administration of quinidine hydrochloride, a change in the Na : K ratio, a fall in plasma quinidine levels and the lactate ion per se explain many of the salutory effects observed.

Comparative Effect of 15 Per Cent Potassium Chloride and 30 Per Cent Potassium Citrate in Cardiac Resuscitation from Ventricular Fibrillation after Acute Myocardial Infarction

Fred Wasserman, Mark W. Wolcott, Curtis G. Wherry, and Leonard Brodsky, Coral Gables, Fla.

There have been few experimental observations on cardiac resuscitation following acute coronary occlusion. The purpose of this report is to elaborate on earlier observations and to compare the relative effectiveness of 15 per cent potassium chloride and 30 per cent potassium citrate in 30 sterile, survival resuscitation experiments.

The chest was opened through a transsternal incision, and the anterior descending coronary artery and vein were ligated together 0.5 cm. distal to the bifurcation. The subsequent large, acute myocardial infarction was easily demonstrable visually and electrocardiographically. Irreversible ventricular fibrillation either followed spontaneously or was induced. Concentrated potassium solutions were injected into both the right and left ventricles, into each ventricle alone or into the proximal portion of the cross-clamped aorta. Once electrical ventricular activity had ceased, massage was instituted and incremental doses of 40 ml. of molar sodium lactate were given intravenously over a period of 4 to 5 minutes. Intravenous l-norepinephrine was infused when necessaary to increase or maintain the blood pressure. Continuous electrocardiograms, arterial pressures, serial arterial pH and serum electrolytes were studied in each procedure.

In all animals with both potassium chloride and citrate we were able to produce ventricular standstill. Subsequently, restoration of cardiac beating occurred more rapidly and with greater facility using 2 to 8 ml. of 30 per cent potassium citrate. Survival animals lived from several hours to six months following successful resuscitation. Histopathologic studies of these animals have demonstrated large transmural myocardial infarctions of various ages.

Study of Electrocardiographic Low Voltage

Richard W. Watts and Kemal Gursal, Cleveland, Ohio

Twenty electrocardiograms showing frontal plane electrocardiographic low voltage (less than 5 mm. in standard and unipolar limb leads) were gathered from 1,756 consecutive electrocardiograms taken on 935 patients in a general hospital. This was an incidence of low voltage in 2.1 per cent of the patients. Notable was the high average age (63 years), the predominance of males (13 of 20), and the high mortality rate (10 of 20).

The etiology of the heart disease was arteriosclerotic in 11 patients, 8 of whom died, thus showing this to be the commonest cause of low voltage. There was no evident cardiac disease in 3. Most striking, not only in our data but in the reports of others, was the lack of correlation of low voltage to heart weight and left ventricular wall thickness. This indicated that electrical activity of the heart was not related to size as has also been shown by atrophic hearts which often have given normal voltage recordings. The lack of correlation was due to the presence of fibrosis and dilatation. This contrasted with the usually good correlation between electrocardiographic evidence of hypertrophy and heart size.

Frontal plane and precordial lead low voltage was compared both in our data and in the reports of others. The lack of additional information with the use of precordial lead criteria was evident so that we recommend that the precordial lead low voltage criteria be abandoned as being of no additional value.

Esophageal Electrocardiography: Reclaimed Diagnostic Method

William H. Wehrmacher and Donald A. Anderson, Chicago, Ill.

Electrocardiograms recorded from multiple levels within the esophagus facilitate diagnosis of obscure cardiac rhythms and reveal the activity of hidden portions of the back of the heart. Simple methods developed in our laboratory provide recordings from 6 different depths within the esophagus rapidly, which range from positions cephalad to the atria through positions caudad to the ventricles, so that the technical difficulties which heretofore harassed clinicians are now overcome. The clinical value of esophageal electrocardiography will be demonstrated by selected electrocardiograms obtained at our hospital during the past 2 years. The esophageal electrocardiogram reveals atrial activity when there is insufficient amplitude for identification in the conventional electrocardiogram. Inadequate amplitude of atrial activity for identification may arise from the failure of the atria to develop sufficient potential, from high electrical resistance between the atria and recording electrodes, from an inappropriate relationship of the atrial vector to the axis of the conventional leads, and from coincidence between atrial waves and portions of the QRS-T complex. The increased amplitude of the atrial activity recorded from within the esophagus may be sufficient to exceed the prominence of the ventricular complexes. When the posterior wall of the left ventricle is projected disadvantageously through ordinary lead connections, the esophageal electrocardiogram will frequently record it with fidelity. It is particularly useful for left ventricular study when the heart is in a vertical position on its anteroposterior axis and its apex is rotated posteriorly upon the horizontal axis.

Clinical Studies on Shock Associated with Bacteremia Due to Gram-Negative Bacilli

Max H. Weil, Los Angeles, Calif., and Wesley W. Spink, Minneapolis, Minn.

Bacteremia has become the commonest single cause of shock other than shock due to myocardial infarction, now being treated on our medical service. A study was made of the clinical features presented by patients from whose blood gram-negative enteric bacteria were recovered. In 11 per cent of a total of 400 such cases, the clinical course was complicated by shock. A procedure performed in the hospital such as instrumentation of the urinary passages or septic complications of surgery was implicated in almost every instance. The history therefore provided an important clue as to the underlying cause of shock. Signs of sepsis followed within 48 hours of the causative event and shock appeared approximately 60 hours after this event. Nausea, vomiting, and diarrhea accompanied the onset of shock. The leukocyte count and percentage of neutrophils were notably increased. A majority of the patients had electrocardiographic abnormalities which made differentiation from myocardial infarction difficult. The mortality rate was 65 per cent with death occurring on an average of 2.7 days after the onset of shock.

Recognition of infection as the cause of shock is of practical importance because the prompt use and judicious choice of antibiotics afford the best opportunity for a favorable outcome. Vasopressor agents, such as metaraminol, provide effective elevation of blood pressure and promote reversibility of the circulatory disturbance. Adrenal cortical hormones depress the manifestations of toxemia caused by overwhelming infection and may be used to gain a period of grace during which infection and shock can be controlled.

Cardiac Output in Response to Exercise in Abnormal Cardiovascular States Using Radioisotopes

Sylvan L. Weinberg, G. Richard Grove, and Robert E. Zipf, Dayton, Ohio

Cardiac output in this study has been determined by external monitoring over the heart of intravenously injected radioiodinated serum albumin (RISA). The method has been standardized in normal individuals and a characteristic rise and fall in cardiac output in response to the Master's test defined. Serial cardiac output determinations were done at rest, immediately, 4.5 and 8 minutes after exercise. With the normal cardiac output exercise response curve as a standard, output curves were observed in 25 patients with cardiovascular disease. These included rheumatic heart disease with mitral stenosis and arteriosclerotic cardiovascular disease with and without congestive failure, angina pectoris, and myocardial infarction.

In both the rheumatic mitral and arteriosclerotic groups the exercise response curve was marked by low resting output values, failure of the expected rise immediately post exercise, and delay in return to resting levels. The degree of deviation from the normal and the characteristics of the actual RISA dilution curve as inscribed on the strip chart recorder varied with the dynamic nature and apparent severity of the disease process but were otherwise not specific. In some instances the character of the curve per se suggested central congestion. Studies before and after mitral commissurotomy revealed changes in output values and in dilution curve characteristics.

It is believed that serial cardiac output studies in response to exercise are of value in various stages of cardiovascular disease in defining severity

in terms of cardiac dynamics and in estimating response to therapy.

Five-Year Follow-Up Study of Men who Returned to Work After a Myocardial Infarction

Morris M. Weiss, Sr., and Morris M. Weiss, Jr., Louisville, Ky.

A five-year follow-up study was made of 431 men who, after their first myocardial infarction, returned to work. All occupations were represented, but the majority were in some aspect of business, either in an executive or sales capacity, in a profession, or were "white collar" workers. Eighty per cent were below the age of 60. Within 5 years, 33 per cent had ceased work through death or retirement. The younger patients worked longer than the older ones. Sixty-seven per cent of the 143 patients who ceased work did so because of death. Return to some form of gainful employment occurred in an average time of 3 months. Complaints of the patient were the best guide towards employment. No single physical finding or test can be a prognostic guide as regards work. None of the patients with another myocardial infarction or who developed heart failure claimed that it was due to their work, which would entitle them to compensation under the Workmen's Compensation Act.

Observations on the Pulmonary Blood Volume Employing a Radioactive Tracer Technic

Arnold M. Weissler, Burley H. McCraw, and James V. Warren, Durham, N. C.

In the interest of developing a simplified technic for assaying alterations in intrapulmonary blood volume, we have investigated a radioactive method employing external monitoring over the anterior chest wall. The method utilizes a sensitive probe scintillation counter with a hexagonal honeycombed collimator attachment and a standard scaling unit. The collimator surface is placed firmly on the anterior chest wall in the second right interspace, and observations are begun 10 to 15 minutes after the intravenous injection of 50 μc. of radioactive iodinated serum albumin. Five 2-minute control counts are obtained before and after each procedure. The total counts recorded under these conditions are a reflection of the volume of blood contained in the region and are not dependent on flow. The collimator affords localization of the monitored area to the pulmonary bed with maximum sensitivity at a depth of 4.0 cm. Validity of changes are tested individually against control readings.

In 16 subjects, alterations in estimated pulmonary blood volume determined by the dye dilution and the radioactive methods compared favorably (mean difference 6 per cent, range 0 to 13 per cent). In 12 normal subjects, the estimated pulmonary blood volume by the present technic fell 28.1 per cent ($p < .01$) 3 to 13 minutes after assuming the standing position. In 10 normal subjects, the estimated pulmonary blood volume diminished by 8.9 per cent ($p < .01$) during 3 to 13 minutes of peripheral blood pooling with pneumatic cuffs. An 11.5 per cent fall in estimated pulmonary blood volume accompanied the Valsalva maneuver in 11 normal subjects ($p < .01$).

It is concluded that the present technic affords a simple device for studying shifts in the pulmonary blood volume.

Vascular Responses in the Human Colon

Jack D. Welsh and Stewart G. Wolf, Jr., Oklahoma City, Okla.

Vascular responses in the mucosa of the human colon were studied in a patient with a colostomy which exposed an area of transverse colon. Direct examination through a dissecting microscope gave indication of the contractile state of small mucosal vessels. The temperature of the colonic mucosa was measured by a Stoll-Hardy radiometer. With relatively little fluctuation in surface moisture, it appeared that variations in the temperature of the colonic mucosa reflected mucosal blood flow. The measurements of colon temperature correlated well with direct observations of mucosal color. Variations of pulse rate plus skin temperature on the dorsum of the hand (Stoll-Hardy radiometer) were also recorded. During quiet observation over a period of from 2 to 3 hours, there occurred a rhythmic rise and fall in colonic temperature, which generally maintained an inverse relation to skin temperature and correlated with the observations of the mucosal blood vessels through the dissecting microscope. During periods of vigorous motor activity in the colon, temperature and color of the mucosa rose and remained high. Following a meal, there also occurred a transitory rise in color and colonic temperature with a dilatation of small vessels near the surface. Again, skin temperature varied inversely with the colon temperature. The pulse rate uniformly increased after eating. Discussions of stressful subjects were followed by a marked increase in colon temperature and color without changing pulse rate or skin temperature. Anticholinergic agents, such as tridihexethyl iodine (Pathilon) given parenterally, induced an acceleration of pulse while colon temperature and color decreased with inhibition of contractile activity. Skin temperature did not change. Thus, a simple method of studying vascular responses in the colon is described. It would appear that the colonic vasculature is influenced by temperature, bowel ac-

tivity, eating, and emotional stress as well as by pharmacodynamic agents.

Variation on Serum Lipids During Mental and Emotional Stress

P. T. Wertlake, A. A. Wilcox, M. I. Haley, and John E. Peterson, Loma Linda, Calif.

A previous study reported by this laboratory described the variation of serum cholesterol in a group of 44 medical students during a control period and in conjunction with the mental and emotional stress of final examinations.

This study has been extended so that 39 of the original group of 44 subjects have now been observed for a second year. Total and esterified cholesterol, phospholipids, alpha and beta lipoproteins have been measured during intervals in which the subjects were relatively free of stress, as well as during the week of final examinations. Psychologic evaluation before and after examination week has been attempted for the purpose of assessing the individual response to a stressful situation of this sort.

Each year the mean level of serum cholesterol for this group of subjects has increased significantly ($p < 0.001$) during the week of final examinations. The increase has been due chiefly to a change in the esterified fraction. Changes in phospholipid, alpha and beta lipoprotein, have been noted but are less consistent. Total serum cholesterol has seemed remarkably labile in certain subjects and this has been of particular interest. We are not able as yet to relate this lability to any particular aspect or severity of stress. The ingestion of safflower oil during a subsequent period of examination stress has reduced the levels but not the degree of change in serum cholesterol.

Coronary Dilatation and Constriction Visualized by Selective Angiography

James W. West and Santiago V. Guzman, Philadelphia, Pa.*

A new technic is presented for selective catheterization of the coronary arteries in conjunction with angiography (roentgenographic and cinematographic methods). This permits direct injection of a radio-opaque dye for evaluating the effects of pharmacologic agents on the coronary vessels in dogs with intact chest. Generally, the local dilator or constrictor effects of drugs upon the coronary vessels are inferred from flow experiments. If a drug increases or decreases coronary blood flow without at the same time causing significant changes in the general circulation, the bed is believed to have undergone dilatation or constriction respectively. Vasodilator and constrictor effects have also been indirectly demonstrated through changes in coronary perfusion pressure, while maintaining flow constant. By means of our technic, an actual visual demonstration of changes in size of individual vessels in the contours of the coronary vascular bed have been observed. Under fluoroscopic guidance, a major branch of the coronary arterial tree (right, left anterior descending, left circumflex) is catheterized in anesthetized dogs by means of a special coronary catheter passed by way of a carotid artery into the aorta and thence into the selected coronary branch. The effect of various types of drugs, namely sympathomimetic, parasympathomimetic, ganglionic stimulating and musculotropic, were studied with this method. Single and serial roentgenograms, as well as cinematograms, have been obtained. The results showed that isoproterenol, norepinephrine, epinephrine, nicotine, acetylcholine and nitroglycerin all dilate the coronary vessels, whereas Pitressin constricts the coronary vessels.

Coronary Lesions in Hormonally-Produced Arteriosclerosis in Rats

Bernard C. Wexler and Benjamin F. Miller, Cincinnati, Ohio

Severe, generalized arteriosclerosis has been produced in female, breeder rats, given ACTH for several weeks. There was no added fat or salt in the diet. In our last report we described some of the great variety of lesions encountered in the aortae of these animals. The coronary lesions are so striking that they merit separate treatment.

One of the earliest changes seen in the coronary vessels is a perivascular "cuffing" produced by all eosinophilic material which cannot be specifically identified as hyalin or fibrinoid. In some coronaries, there is an eccentrically located intimal hyperplasia accompanied by lysis of elastic fibers and concomitant dilation of the vessels. In other animals, intimal and medial hypertrophy, with or without giant foam cells, was observed to cause virtual obliteration of the lumen. Other coronary lesions consist of calcification of the intima, which may sometimes be accompanied by elastosis and dilatation. This calcific involvement is especially severe where the coronary vessels originate from the aorta. Metastatic calcification and cartilaginous metaplasia are found in the coronary arteries, but no area of dystrophic calcification such as seen in the aorta. Occasional coronary vessels display intimal hyalinization without involvement of the medial and adventitial layers.

The epicardial branches appear to be more severely involved. Aside from the occasional foam cells in the occlusive variety, the many different pathologic lesions contain very little lipid. Only rarely have we encountered myocarditis or myocardial lipidosis. These hearts are greatly en-

lar; d with pronounced left ventricular hypertro hy.

Ele rocardiographic Differentiation of Anterior Myocdial Infarction from Left Ventricular Hypertrophy: e "Sloping Shoulder" Sign

erald H. Whipple, Boston Mass.

It is often difficult to distinguish electrocardiogr hically between old anterior myocardial infarctio and left ventricular hypertrophy, even with spe ial leads. A new electrocardiographic criterio for detecting infarction is reported. The electro rdiograms of 3,000 consecutive patients were rev ewed to find those which showed QS deflections in leads V_1 and V_2, or in V_1 through V_3. To concentrate difficult cases, tracings with notching of the first part of the downstroke or with initial upward QRS complex deflections in leads farther to the right were excluded, as were those with QRS complex durations over 0.10 seconds. The time which elapsed from onset to completion of the first 1/3 of the total amplitude of the QS downstroke in V_1 through V_3 was carefully measured in the remaining 41 cases. Independent analysis of clinical and available autopsy data divided the 41 cases into those in whom coronary artery disease was doubtless present (group A, 19 cases), those in whom it was unlikely (group B, 10 cases), and uncertain cases (group C, 12 cases).

As measured above, greater initial slurring of the downstroke ("sloping shoulder") in group A compared to group B was found to be statistically significant in all 3 right precordial leads, whether or not evidence for coexistent left ventricular hypertrophy was present. Separation of groups A and B was particularly sharp in V_2; only 3 group A cases showed downstroke times less than 0.03 seconds, while in group B the time exceeded 0.025 seconds in only 1 case. Other considerations permitted still further electrocardiographic separation.

Central and Peripheral Venous Pressure Correlations with Emotional Stimuli

Kerr L. White, Dan A. Martin, Charles R. Vernon, and David H. Jones, Chapel Hill, N. C.*

Influences of emotional stimuli on venous circulation were observed in 3 studies: 1. Central venous pressure (CVP) was recorded continuously in 14 patients (one duodenal ulcer, 13 congestive heart failure (CHF) through a polyethylene catheter and Statham transducer, simultaneously with respiration (pneumotachygraph), EKG (lead II), and psychogalvanic skin response (PGSR). Following control recordings of physical maneuvers, emotional stimuli predicted to be "stressful" or "neutral" were recorded. "Stressful" questions, derived from previous medical interviews which reflected disturbing emotional experiences, correlated with CVP increases and were predicted successfully 39/70 times ("neutral" questions, 10/31; $p < .05$). 2. CVP fluctuations, including cumulative effects of successive emotional stimuli, were recorded for 1- to 2-hour periods in 14 patients while silent and resting and in 10 during psychiatric interviews. Rapid increases in CVP up to 60 mm. H_2O in 6 minutes and acute rises of 35 mm. H_2O occurred with emotional stimuli. Follow-up interviews with a psychiatrist of 28 CHF patients indicated that disturbing life situations had indirect deleterious influences on cardiac compensation in 12, direct influences in 19, and no apparent influences in 5. 3. Venous tone reflected in peripheral venous pressure (PVP) of isolated forearm vein segments (recorded simultaneously with respiration, EKG, and PGSR) was studied in 5 healthy volunteers. Nonspecific "stressful" stimuli correlated significantly ($p < 0.5$) with increases in PVP of as much as 80 mm. H_2O (mean 31 mm. H_2O) over control responses. Similar "stressful" stimuli produced characteristic patterns, and highly significant ($p < 0.1$) increases in duration of elevated PVP over control responses.

Effectiveness of an Oral Penicillin Prophylaxis Program in Treatment of Rheumatic Fever Over a Period of Ten Years

Ruth Whittemore, New Haven, Conn.

This report presents 10 years of experience with oral penicillin prophylaxis in the treatment of rheumatic fever recurrences, together with a study of certain practical aspects. As of June 1, 1958, 4,885 children and adults were receiving 250,000 units of penicillin G daily in the State prophylaxis program.

Patient participation was studied in several groups. Returns of filled prescriptions and distribution of State penicillin revealed that only 33 per cent (1,388) of the 4,200 patients registered 1 year ago were delinquent. A detailed study of family influence on patients under 12 years from 80 random families, however, indicated that 45 per cent (36 patients) were not faithful. In this study, patient participation was correlated specifically with the mother's ability to understand the need for penicillin together with her concept of the physician's opinion of her. At the inception of the adolescent cardiac clinic in 1955, 1/3 of the patients over 14 were taking penicillin, but 3 years later, in spite of more educational efforts and attempts to understand this age group, 49 per cent (94 of 195 patients) were still delinquent.

Recurrences of rheumatic fever have been incompletely reported since 1955. However, 10 of the 12 childhood recurrences during this time were

traced to streptococcal contacts in the home. This raises the question of the adequacy of a single daily tablet.

These studies indicate that a more effective oral prophylactic program can be achieved through more concentrated educational efforts by physicians, clinic and public health personnel, and by a better understanding of the patient and his family.

Extracellular Fluid and Plasma Volume Changes in Nonedematous Hypertensives After Prolonged Treatment with Chlorothiazide

Ilse M. Wilson and Edward D. Freis, Washington, D. C.

Some question remains as to whether the reductions in plasma volume (PV) and extracellular fluid space (ECF) following chlorothiazide are transient phenomena or are maintained throughout prolonged treatment. This question needs resolution because of its possible role in the mechanism of the blood pressure reduction.

Eleven compensated, nonedematous, hypertensive patients were studied repeatedly over periods of 3 to 8 months (average 6.3 months) of treatment. All maintained some reduction of mean blood pressure averaging 15 per cent. At the end of the treatment period, 8 of the 11 exhibited a reduction of ECF greater than 1 liter, with averages of −3.2 L. for SCN and of −2.5 L. for $S^{35}O_4$ spaces. The reduction in PV averaged 15 per cent immediately after chlorothiazide and 8 per cent at the end of treatment. The hematocrit remained slightly elevated in 10 of the cases (average 2 points above control).

During treatment, serum concentrations of sodium and chloride did not change significantly, whereas potassium fell (average 17 per cent).

Two weeks after discontinuing treatment, all patients showed some elevation of mean blood pressure (average 16 per cent). This was accompanied by an average rise of PV of +9 (range +.2 to +26) per cent and ECF of +9 (range 0 to +27) per cent. None showed decreases.

These data support the conclusion that chlorothiazide, even in nonedematous patients, removes a fraction of ECF, which loss is partially or completely maintained so long as the patient continues to take the drug.

Short-term Hormone Therapy and Prevention of Rheumatic Heart Disease

May G. Wilson and Wan Ngo Lim, New York, N. Y.

This study is concerned with the cardiac status of 82 patients, 4-19 years of age, who received short-term hormone therapy during the years 1949-1958 for 100 attacks of active carditis of varying duration.

Forty-nine were initial attacks and 51 recurrent. The duration of carditis before therapy was less than 10 days in 58 per cent, less than 1 month in 33 per cent, and 1-4 months in 9 per cent. Hormones were given for an average period of 7 days and stopped abruptly. These included corticotropin, cortisone, hydrocortisone, prednisone and prednisolone.

In 91 per cent of the patients with active carditis of less than 1 month's duration, there was no overt clinical evidence of residual cardiac damage in initial attacks, or increased damage in recurrent attacks. The children were ambulatory 2 to 3 weeks after the onset of therapy, and have maintained their cardiac status as noted at the end of therapy in the absence of recurrent attacks for periods of 6 months to 8 years.

Progressive symptoms of carditis were arrested when the duration of carditis was longer than 1 month. However, there was little influence on the residual cardiac damage sustained before the institution of therapy.

It is concluded that overt residual cardiac damage was prevented in patients with active carditis by early adequate short-term hormone therapy.

Studies of the Content and Distribution of Sodium, Potassium and Water in Arterial Hypertension

Bertram M. Winer, Boston, Mass.

Twenty-four-hour exchangeable sodium and potassium (Na_e and K_e), extracellular fluid (thiosulfate space), total body water (antipyrine space), and plasma volume (I^{131} serum albumin) were determined in 28 patients with essential hypertension and 24 control subjects. Congestive failure, renal insufficiency, and drug therapy were excluded. There were no significant differences between the groups in Na_e, K_e, extracellular fluid, or plasma volume per Kg. of body weight or per liter of body water.

The effects of 0.75–1.5 Gm. of chlorothiazide daily for 6 to 8 weeks were studied in 18 hypertensive patients. Mean serum potassium fell from 4.1 to 3.4 mEq. per L. ($p < .01$). No significant changes in mean serum sodium, exchangeable sodium, exchangeable potassium, extracellular fluid, total body water, or plasma volume, were observed; 4 patients, however, lost more than 400 mEq. of potassium and 2 more than 400 mEq. of sodium. There was no correlation between change in electrolyte or water and change in blood pressure. Blood pressure was not altered by the subsequent addition of 135 mEq. of sodium or 106 mEq. of potassium daily.

The effects of rauwolfia were examined in 4 selected hypertensive patients. Exchangeable sodium increased more than 150 mEq. in each, although blood pressure was lowered or unchanged during administration.

These findings suggest that (1) a defect in sodium metabolism is not a primary pathogenetic factor in essential hypertension; (2) the hypotensive effect of chlorothiazide is not dependent upon its saliuretic effect; (3) rauwolfia can exert a sodium-retaining as well as a hypotensive effect; and (4) moderate changes in exchangeable sodium may not strongly influence blood pressure.

Validity of Qualitative Direct Body Ballistocardiography in Cardiac Evaluation: Significance of "Acceleration" and Criteria for Differential Diagnosis

Nahum J. Winer, New York, N. Y.

Direct body ballistocardiography is a valid adjuvant to electrocardiography, despite quantitative shortcomings and qualitative inconsistencies. Method: Dock shin-bar technic recording head-foot displacement, velocity, acceleration (Arbeit d-v-a) during breathing and midinspiration. Acceleration is emphasized because as fourth derivative of "micrroscope" displacement it records the favored higher frequencies which ultra-low frequency methods may obscure.

Conclusions: 1. the ballistic complex has organic, myocardial and functional vascular elements. HI reflects the nature of systole; IJK, the residuum of systole plus the systemic vasculature. 2. Aberrations may be (A) functional, due predominantly to "splanchnic pooling." HI is relatively intact, IJK deteriorated, is corrected by midinspiration, abdominal binder or, varyingly, exercise despite persistent ECG "ischemia," (B) organic, reflected by (a) ischemia, (b) failure, (c) infarction. The first 2 resemble the "functional," but are uncorrected by midinspiration. Vasodilators correct ischemia; digitalization, failure. Acute infarction effects HI deterioration with or without IJK alteration, is not corrected by midinspiration, improves inversely to ECG retrogression. This has proven diagnostic even without pain or other laboratory evidence. Common to all is increased respiratory variation, reflecting a diminished pulmonic "buffer."

Cases: 1. Functional deterioration corrected by midinspiration. 2. Depleted pulmonic "buffer," "organic" in displacement, "functional" in acceleration. 3. HI deterioration of infarction improving with ECG retrogression. 4. Preinfarction electrocardiographic "ischemia" effecting IJK deterioration, aggravated by exercise. 5. Same with subsequent exitus transiently improved by rauwolfia and erythrol tetranitrate ballistocardiographically, despite continued ECG retrogression. 6. Ballistocardiographic "ischemia" without symptoms, of possible mixed "organic" and "functional" origins, corrected by erythrol tetranitrate but not midinspiration. 7. Ballistocardiographic "ischemia" of "functional," possibly vasospastic, origin aggravated by exercise, counteracted by ergot derivatives.

Changes in Blood Cholesterol and Atherogenesis in Roosters by Exercise and Androgen on Plain Mash After an "Atherogenic Diet"

Harry Y. C. Wong, Joseph E. Anderson, Jr., Tatsuo Kimura, and Frank B. Johnson, Washington, D. C.

Previous reports from our laboratory indicate that exercise and testosterone propionate, either singly or in combination, caused a significant reduction in the blood cholesterol and a subsequent diminution of severity of aortic and coronary atherosclerosis. The present study was undertaken to study the effects of exercise and testosterone propionate on blood cholesterol changes and the development of atherosclerosis of the aorta and coronary arteries of roosters on plain mash after having been on an "atherogenic" diet of 2 per cent cholesterol and 5 per cent cottonseed oil. There were 2 phases to the experiment: During the first phase all of the groups were fed a high cholesterol diet for 8 weeks. The second phase consisted of 9 weeks during which time plain mash was fed to all birds. Significant reduction in the blood cholesterol levels were observed by the second week after removal from the high "atherogenic" diet. The difference in the rate of fall of blood cholesterol in the exercised and nonexercised groups, whether treated with testosterone or not, did not seem significant. There were gross evidences of regression in the amount of atheromatous plaques in all groups fed an "atherogenic" diet as compared to the birds before being placed on "plain mash."

The foregoing results seem to indicate that removal of a 2 per cent cholesterol and 5 per cent cottonseed oil regimen resulted in: 1. decrease in blood cholesterol to normal values within 5-6 weeks. Factors, such as exercise and testosterone propionate, do not seem significantly to alter the rate of fall of the blood cholesterol levels. 2. There were gross evidences of regression of the severity of atherosclerosis of the aorta.

Indicator-Dilution Method for Simultaneous Measurement of Pulmonary and Systemic Blood Flow in Patients with Left-to-Right Shunts

Earl H. Wood, Hiram W. Marshall, Newton C. Birkhead, James L. Russell, and André David, Rochester, Minn.*

Maximal sensitivity for detection of a left-to-right shunt is provided by dilution curves recorded

from the right side of the circulation at sites downstream to the defect with injection of indicator into a distal pulmonary artery, or left heart at a site upstream to the shunt. The position of the defect can be localized by: (1) multiple dilution curves from the right heart recorded at sites upstream *and* downstream to the defect with injections at a site downstream to the defect; or (2) multiple dilution curves from the right heart at a site downstream to the defect with multiple injections into the left heart at sites upstream *and* downstream to the defect. The shunted fraction ($F_{L\text{-}R}$) of pulmonary flow is equal to the ratio of the areas of the forward-triangle portions of the curves recorded simultaneously from the right side of the circulation and systemic artery (SA). These areas are calculated from the equation: $A = BT \cdot C_p/2$, in which BT and C_p are the build-up time and peak deflections of the respective curves. Pulmonary and systemic flows are calculated from the equations: Q_p–47 I/ $(C_p \cdot BT)_{SA}$ and $Q_S = Q_p \cdot (1-F_{L\text{-}R})$ respectively.

Satisfactory agreement is obtained between blood flow and shunt values calculated by these equations and by conventional Fick methods. The simultaneous right-heart and systemic-artery dilution curves of cardio-green encompass a period of less than a minute. Measurements and calculations of blood flow therefrom can be completed within minutes.

Rate of Decline in Myocardial Glycogen Following Arrest of Coronary Circulation: Effect of Pretreatment with Glucose and Insulin

John C. Wood, Guillermo S. Morales, and Hadley L. Conn, Jr.,† Philadelphia, Pa.*

Experience indicates that in the stopped heart, 30 minutes represents the approximate upper limit of circulatory interruption compatible with functionally adequate recovery. The factor(s) governing this time limit have not been demonstrated. Under anaerobic conditions, myocardial energy requirements presumably must be satisfied by glycolysis. Cardiac glycogen stores, therefore, merit consideration as such a limiting factor. Glycogen content as a function of time was determined in 11 arrested, nonperfused dog hearts maintained at 37.5 C. (untreated). Parallel studies were done on 9 hearts arrested after an infusion of 5 Gm. per Kg. of 50 per cent glucose, containing 3 units of insulin per Kg. given to the intact animal (treated). Initial mean glycogen content was significantly greater in the treated (850 mg. per 100 Gm.) than untreated (428 mg. per 100 Gm.) group, and remained significantly greater throughout a 2-hour period of observation. After 60 minutes of arrest, glycogen content in the treated hearts averaged 402 mg. per 100 Gm., in contrast to 69 mg. per 100 Gm. in the untreated. In both groups the rate of glycogen disappearance was reduced after 30 to 60 minutes. Only in the first 30 minutes in the treated hearts did the rate of decline (if equated with myocardial consumption) suggest energy production in the range indicated by the QO_2 of the arrested perfused heart.

The studies show that, in the absence of perfusion, canine myocardial glycogen is largely depleted within 1 hour. Initial glycogen content can be increased and its subsequent anoxic depletion delayed by preliminary infusion of glucose and insulin.

Normal Vectorcardiogram and Geometrical Derivations

Zang Z. Zao, Galveston, Texas

A resistance network is constructed for the Wilson tetrahedron based on the Burger equation. This equation was established from experimental data, both from normal human subjects and a heterogenous human phantom.

At the RLF plane, the long axis of the normal QRS loop recorded with this network differed from that without. With this network the long axis showed better correlation with the heart axis by teleradiogram, and this better correlation held true in normal respiration, deep inspiration, and deep expiration.

Two triaxial reference systems have been constructed from the Wilson tetrahedron in image space; one for the RLF plane for bipolar leads RL, RF, and LF, and one for the RLB plane for bipolar leads RL, RB, and LB. Each axis represents the corresponding lead vector direction, and its division is inversely related to the lead vector length. The successive plotting of a vectorcardiogram can be done in either system in the usual way from 2 corresponding lead data.

Comparative curves have been constructed for the RLF plane and LRB plane. These were derived from the above 2 reference systems on the one hand, and the Einthoven triangle and the equilateral RLB triangle on the other hand. Each curve represents the function of the quotient of 2 lead projections with respect to direction.

By means of comparative curves, the QRS long axis in the Wilson tetrahedron can be predicted at once if it has been recorded in that with the network, and vice versa. This prediction was excellent at the RLF plane and satisfactory at the RLB plane. The same held true for the T long axis.

This study implies the desirability of constructing individual Wilson tetrahedron from cardiac patients, and emphasizes the need of clarifying the role of human tissue conductivity before any vectorcardiographic system can be generally accepted.

Wolff-Parkinson-White Syndrome: A Benign Finding?

Walter T. Zimdahl, Buffalo, N. Y.

Because of the growing custom of obtaining electrocardiograms, the syndrome of a short PR interval and long QRS is being recognized with increased frequency. Collecting a series of 40 cases for the past 10 years, we have been impressed on several occasions that this syndrome is not always a benign one. Only 7 of these were females. Although it is true in most cases observed that the patient is a healthy individual, a mistaken diagnosis of heart disease is made in almost one half the patients. In 15 of our 40 cases there has also been some evidence of definite associated heart disease. Three of the patients in whom this syndrome was discovered at an early age gradually outgrew the need for quinidine and the episodes of tachycardia gradually decreased or ceased, even though they remained in their aberrant complexes. One of our patients developed a supraventricular tachycardia with aberrant conduction and a ventricular rate of over 300. He was admitted in a shock-like picture. In the present series, there has been observed attacks of syncope, coma, unconsciousness, sudden death and severe iatrogenic heart disease. By far the most important cause of error is in misinterpretation of the electrocardiogram and several of our patients have developed severe iatrogenic heart disease. Symptoms in this syndrome occur exclusively in the progress of paroxysmal tachycardia or during its onset or offset. In any given patient, the diagnosis may call attention to the possibility that paroxysmal tachycardia is the explanation of an obscure clinical picture. Quinidine and atropine in a proper dosage schedule are the two most valuable drugs in diagnosis.

Inadequacy of Closed Mitral Commissurotomy to Correct Mitral Stenosis

Henry A. Zimmerman and Jorge Martens de Oliveira, Cleveland, Ohio

For some time, both in our group and others, we have been concerned with the study of hemodynamics both before and after a period of time following mitral commissurotomy. On the whole, these studies have been disappointing as they show little or no improvement. Heart size, as a rule, has increased.

A series of 25 cases of mitral stenosis with commissurotomy were reviewed. Twenty of these cases died at intervals up to 2 years following surgery. Studies were made to determine the adequacy of the resulting opening of the mitral valve. The remaining 5 cases were re-operated with the open technic allowing a close inspection of the mitral valve.

In the entire series an inadequate opening of the valve area was quite apparent and it would appear that little or nothing was accomplished in the improvement of the patient's hemodynamics.

It is apparent that the only way to achieve a successful adequate opening of the mitral valve is by open cardiac surgery.

Percutaneous Right Heart Catheterization, Using Polyethylene Tubing

Lenore R. Zohman and M. Henry Williams, Jr., Valhalla, N. Y.

A polyethylene tube may be passed through a thin-walled 14-gage needle in a basilic vein into the right heart and pulmonary artery, using intracardiac electrocardiographic control. The intracardiac electrocardiogram is obtained by conduction through a column of 5 per cent saline led off to an electrocardiograph monitor by a wire attached to the needle outlet of the saline infusion bottle. This arrangement not only affords chamber localization, but warns of contact of the catheter tip with the endocardium, advises of location of the catheter within the coronary sinus and detects catheter coiling within a chamber when the proper sequence of EKG patterns is reversed as the catheter is advanced.

This technic has been used without complications in 75 patients. In the last 38 consecutive cases, the pulmonary artery was catheterized in 24 patients and the right ventricle in 8. Once the catheter entered the atrium, it entered the pulmonary artery in 75 per cent and the ventricle in 100 per cent of the cases. Failures were due to sharp angulations of the veins or venospasm.

This method is not applicable where visualization of the catheter tip is important for diagnostic purposes, is more liable to limitation by the anatomy of the veins of the arm than a procedure performed with a more rigid nylon catheter and is contraindicated in patients who cannot tolerate intravenous administration of 150 ml. of 5 per cent saline. It has distinct advantages in selected cases, however, because it replaces a cutdown with a venipuncture, eliminates fluoroscopy, and makes possible repeated catheterization through the same vein.

Treatment and Prevention of Ventricular Fibrillation in Stokes-Adams Disease

Paul M. Zoll, Arthur J. Linenthal, Raphael B. Reider, William Gibson, and Leona R. Norman, Boston, Mass.

Ventricular tachycardia and fibrillation, important mechanisms of syncope and death in patients with A-V block, present difficult problems in treatment and prevention.

We have twice successfully resuscitated patients from syncope due to ventricular tachycardia by the external application of 60-cycle alternating current of 360 to 450 volts for 0.15 second across large electrodes on the chest. With similar countershock currents we have repeatedly resuscitated the same 2 patients from episodes of ventricular fibrillation, one 10 times and the second 300 times. Though theoretically simple, this technic involves the considerable practical problems of immediate recognition of the mechanism of the seizure and prompt application of external countershock. The safety of this technic is shown by the absence of recent myocardial or pericardial injury or scarring in the second patient, who died at home 6 weeks after the last defibrillation.

For prevention of recurrent tachycardia or fibrillation, we have found drugs that accelerate the idioventricular rate (epinephrine, isoproterenol, ephedrine) occasionally useful, but more often ineffective, and at times dangerous by increasing multifocal ventricular activity. Drugs that depress ventricular rhythmicity (quinidine, procaine amide, potassium), we have found, always increase multifocal ventricular activity; we consider them absolutely contraindicated in patients with Stokes-Adams disease.

In 8 patients ventricular acceleration by external electric cardiac stimulation provided a safe and effective, although temporary, means of preventing tachycardia and fibrillation. Rates of stimulation required to suppress multifocal activity, determined repeatedly and precisely, varied from 45 to 110 beats per minute.

Lipid and Acid Polysaccharide Relationship in Human Aortas

Frederick T. Zugibe and Kenneth D. Brown, Downey, Ill.

The relation between acid mucopolysaccharides and lipids in the early pathology of atherosclerosis is an area of controversy. A new carbowax embedding technic, which retains lipid in *statu nascendi*, has permitted the observation of both lipid and acid mucopolysaccharides in a single tissue section. Routine stains have been applied to adjacent sections. Utilizing this embedding technic and a combination staining procedure for these substances, studies have been made of aortas of individuals ranging in age from fetal age to 40 years. The following is a preliminary report of our observations:

In the fetuses, essentially no lipid was present. Reduplication and fraying of the internal elastic membrane was observed in most cases. No correlation was noted between acid mucopolysaccharide deposition and these changes in the internal elastic membrane. In infants, lipid was occasionally observed as isolated droplets in the intima. No relationship was observed between acid mucopolysaccharide, lipid and/or fragmentation, fraying and reduplication of the internal elastic membrane. In juveniles and adults there was a correlation between acid mucopolysaccharide and elastic changes. This, however, appeared to be due to the deposition of supportive collagen rather than acid mucopolysaccharide deposition per se. Isolated lipid infiltration of the internal elastic membrane and its reduplicated and fragmented elements was a consistent finding. However, there was no observed correlation between acid mucopolysaccharide and lipid.

Sensitivity of Electrocardiography in the Detection of Heart Disease

William J. Zukel, Bethesda, Md., Robert B. McGandy, Joseph T. Doyle, and Ralph W. Reynolds, Albany, N. Y.

Electrocardiography has been shown to be the single most valuable tool for diagnosing heart disease in adult population surveys. In the present study, the interpretation of electrocardiograms of 1,000 males, 40-54 years of age, has been compared to the clinical diagnoses based on a complete cardiovascular evaluation. This group is a part of the Albany epidemiologic study of cardiovascular disease and has been followed annually for 5 years. The first year's electrocardiograms were read independently by three readers and were classified on the basis of the following lead combinations: lead I; leads I-III; I-aV_F; I-V_{12}.

The detection of verified heart disease by 3 readers ranged from 40-54 per cent interpreting lead I alone to 62-66 per cent for all 12 leads. The number of abnormal tracings in persons clinically normal (false positives) tended to increase with the number of leads read, reaching 7-16 per cent with 12 leads. Classification of these electrocardiograms by the 3 readers was very similar.

This study has provided the opportunity to assess the future implication of so-called false positive ECG's over a 5-year follow-up period. The subsequent rate of new heart disease in persons with a normal ECG at the first examination was 30 per 1,000 over the 5-year period. By contrast, the new disease rate was 150 per 1,000 in our group of false positives. This represents an approximately threefold increase in case finding rate over that of 60 per 1,000 in adult males with an elevated serum cholesterol.

MEDICAL MOTION PICTURES

DAILY PROGRAM

OCTOBER 24 to 26, 1958

(Shown in room at back of Larkin Hall)

9:30 A.M. to 12:00 Noon

9:30 **William Harvey and the Circulation of the Blood** (Color, Sound)
Royal College of Physicians, Sir Henry Dale, London, England (1957)

10:20 **Techniques in Angiography** (Color, Sound)
A. W. Humphries, M.D., Cleveland, Ohio (1957)

10:40 **Jugular Venous Pressure: A Method of Measuring Central Venous Pressure at the Bedside** (Color, Sound)
Michael B. Matthews, M.D., Edinburgh, Scotland and David G. Greene, M.D., Buffalo, N. Y. (1958)

11:00 **Double Anterior Left Heart Puncture** (Color, Sound)
David G. Greene, M.D., Buffalo, N. Y. (1958)

11:15 **Development of the Heart** (Color, Sound)
George H. Humphreys, II, M.D., New York, N. Y. (1957)

2:30 P.M. to 5:00 P.M.

2:30 **The Mitral Valve—Dynamic Pathology and Surgery** (Color, Sound)
Robert P. Glover, M.D., Julio K. Davila, M.D. and Robert G. Trout, M.D., Philadelphia, Pa. (1957)

2:45 **Correction of Aortic Regurgitation by Bicuspidization of the Valve**
Charles P. Bailey, M.D., Philadelphia, Pa. (1958) (Color, Sound)

3:15 **Thoracoabdominal Aneurysm Involving Celiac, Superior Mesenteric and Renal Arteries** (Color, Sound)
Michael E. DeBakey, M.D., Denton A. Cooley, M.D., George C. Morris, Jr., M.D., Houston, Texas, and Oscar Creech, Jr., M.D., New Orleans, La. (1956)

:40 **Just Four Minutes: Resuscitation for Cardiac Arrest*** (Color, Sound)
Lenore R. Zohman, M.D., Valhalla, N. Y. (1958)

:10 **Anomalies of the Heart** (Color, Sound)
George Humphreys, II, M.D., New York, N. Y. (1958)

*Premier Showing

SCIENTIFIC EXHIBITS

All Exhibits Will be Displayed in the Civic Auditorium

Los Angeles County Heart Association Artery Bank. *Chauncey A. Alexander, Los Angeles, Calif.*

Operating exhibit of latest artery bank equipment and technics used for processing and preserving human arteries for use as homografts.
(Booth 2)

The Blood of Man. *American Association of Blood Banks, Miami, Fla.*

This exhibit is directed towards stimulation of interest in the availability of blood donors and describes the many blood products available and their therapeutic uses. It further describes the role which the American Association of Blood Banks plays in making effective use of blood banking practice through the dissemination of current transfusion concepts.
(Booth 1)

Hypertension: Newer Aspects of Therapy and Effects Upon Vascular Deterioration. *John R. Beem, Nelson H. Schimmel, Leonard M. Dreifus, James B. Donaldson, and John H. Moyer, Philadelphia, Pa.*

This exhibit demonstrates the effect of blood pressure elevation upon vital vascular beds, and the modification of these responses by reducing blood pressure with various methods of therapy. It also outlines the effects of drugs which alter sympathetic nervous system activity, and the manner in which these responses are influenced by salt depletion through the use of diuretic agents which have recently become available.
(Booth 11)

Wedge Pulmonary Arteriography. *A. L. Loomis Bell, Jr., Seiichi Shimomura, and John A. Taylor, Jr., New York, N. Y.*

Radiopaque dye injected through a cardiac catheter wedged in a small pulmonary artery outlines the pulmonary vascular pattern. This pattern is correlated with the abnormal hemodynamics and histology in patients with congenital and acquired cardiac defects.
(Booth 16)

Intracardiac Electrocardiography in Man. *Charles A. Bertrand, Lenore R. Zohman, and M. Henry Williams, Jr., Valhalla, N. Y.*

The exhibit stresses the use of intracardiac electrocardiography as a routine adjunct to cardiac catheterization (based on a study of 136 patients). Normal standards are presented and these show the localizing value of the intracardiac electrocardiogram. The major advantages of this technic are the evidence of endocardial trauma, unrecognized coronary sinus catheterization, prompt recognition of arrhythmia and decreased exposure to radiation.
(Booth 3)

Cinefluorography and X-Ray Image Amplication. *David W. Cugell, M. Mostafa Abdel-Fattah, Margaret E. Gantt, William B. Buckingham, and John E. Jacobs, Chicago, Ill.*

A new type of x-ray image amplifier with a 12-inch diameter circular viewing area that permits the remote location of multiple viewing screens and recording camera will be displayed. It operates at conventional fluoroscopic radiation dosages. Physiologic and clinical studies using cinefluorography will be demonstrated.
(Booth 7)

Post-Graduate Medical School of the New York University—Bellevue Medical Center. *Clarence E. de la Chapelle, Associate Dean, New York, N. Y.*

The Post-Graduate Medical School offers opportunities for graduate and post-graduate education in all branches of medicine and surgery.
(Booth 24)

Coronary Visualization by Occlusion Aortography during Induced Cardiac Arrest in the Intact Subject. *Charles T. Dotter, and Louis H. Frische, Portland, Oreg.*

Thoracic aortography is unsatisfactory for demonstrating man's coronary arteries due to the opposing effects of aortic blood flow. Such effects are eliminated by injecting contrast agent during a brief period of induced cardiac arrest and total occlusion of the ascending aorta. Evidence of the effectiveness, simplicity, and safety of this technic is presented.
(Booth 10)

Cardiovascular Case Progress Index. *Lawrence Z. Feigenbaum, Nancy T. Maser, and Malcolm S. M. Watts, San Francisco, Calif.*

The exhibit demonstrates a cardiovascular index operating at the University of California School of Medicine. Patients with cardiovascular disorders are registered with the index. All registered and follow-up data are punched on IBM cards. Patients or clinical data for teaching and research can be located. There has been 98 per cent follow-up.
(Booth 4)

Prevention of Paroxysmal Tachycardia with Antithyroid Medication. *Henry L. Jaffe, Herbert Gold, John H. Williams, and Eliot Corday, Los Angeles, Calif.*

Thirty-three patients with recurrent tachycardia were treated with radioactive iodine and propylthiouracil and observed for a period of as long as 6 years. The induction of a hypometabolic state with radioiodine produced excellent results in 28 patients. Radioactive iodine is a preferred method of inducing hypothyroidism for the prevention of recurrent auricular and ventricular tachycardias.
(Booth 19)

Metal Concentrations in Cardiac Tissue. *George C. Griffith, Balakrishna Hegde, Edward M. Butt, and Robert W. Oblath, Los Angeles, Calif.*

Thirteen trace metals were studied in cardiac tissues of patients with: (1) acute myocardial infarction; (2) acute and chronic myocardial infarction; (3) chronic myocardial infarction; (4) coronary atherosclerosis without infarction; (5) idiopathic hypertrophy; (6) endosclerosis; (7) amyloidosis; and (8) for comparison, normals. Our investigation shows that metals in various diseases affecting the heart appear in definite patterns; this will be illustrated in the exhibit.
(Booth 20)

Cardiovascular Dynamics of Bowel Function. *Alfred Halpern, New York, N. Y., Norman Shaftel, Brooklyn, N. Y., and David Selman, New York, N. Y.*

Death after straining associated with defecation is not rare. Several mechanisms involving the circulation of the heart, pulmonary and peripheral vessels have been suggested in explanation. This exhibit describes the circulatory dynamics observed during defecation in both normal and constipated patients. The data obtained from several hundred patient measurements describe the elevation of intrathoracic pressure occurring during straining and its consequent effects on the blood pressure, electrocardiogram circulation time, and the heart rate. Approximately 11 per cent of the efforts of normal subjects were of sufficient magnitude and duration to initiate the classic Valsalva effects of the circulatory system. This incidence was increased approximately fivefold among the constipated subjects. A systemic study of the circulatory effects associated with defecation points toward several methods of avoiding these responses.
(Booth 13)

Theory, Technic and Application of Indicator Dilution Methods. *W. W. Lacy, E. V. Newman, L. H. Ramsey, P. Latimer, T. G. Arnold, and B. Moore, Nashville, Tenn.*

Charts of the mathematical analysis, technic of sampling and recording, and the application of indicator dilution curves will be presented. A functioning circulatory model will be used to demonstrate injection and sampling systems and effect of variation in volumes, flow and valvular incompetence on dilution curves.
(Booths 17 and 18)

Cycloidal Vectorcardiography. *David C. Levinson, Los Angeles, Calif.*

Three planes of the vectorcardiogram and an electrocardiogram are recorded simultaneously on a 17″ oscilloscope through a specially designed 4-channel electronic switch. The vectorcardiograms slide electronically, horizontally and vertically, permitting separation of P, QRS, ST and T vectors. The sliding feature permits registration of vectors of arrhythmias. Illustrations are presented.
(Booth 21)

Surgical Anatomy of the Coronary Arteries. *Angelo M. May, San Francisco, Calif.*

The exhibit shows charts and models depicting the variations of the anatomy of the coronary arteries as observed in 200 autopsy specimens and 300 skiagrams of Schlesinger injected human hearts. Illustrations and specimens of atheromas removed from coronary arteries, their type and location, and illustrations of the various current surgical approaches are included.
(Booth 22)

The Farmer with Heart Disease. *W. H. M. Morris, L. S. Hardin, J. E. Wiebers, and R. L. Eichhorn, Lafayette, Ind.*

The Purdue Farm Cardiac Projects. Some work and environmental stresses of the farmer are shown. The response of farmers to coronary heart disease in terms of work load is illustrated. The incidence of fatality certified from heart disease is compared for farm and nonfarm white males.
(Booth 9)

Drug Therapy of Hypertension. *Marvin Moser, White Plains, N. Y., and Alice I. Macauley, Valhalla, N. Y.*

The results of treatment in a 4 to 5 year period of over 150 patients with essential and renal hypertension are presented. Combination drug therapy with the rauwolfia drugs, hydralazine, chlorothiazide, and the ganglionic blocking agents, pentolinium and mecamylamine, appears to be effective in over 50 per cent of cases. Evidence that suggests decreased morbidity and a prolonged survival time in the treated group is presented. Practical management of the patient is stressed.
(Booth 14)

Effects of Mephentermine. *M. J. Oppenheimer, P. R. Lynch, and G. H. Stewart, Philadelphia, Pa.*

This exhibit demonstrates the changes in the fundamental properties of heart muscle which are produced by mephentermine and illustrates how these changes in refractory period, conduction velocity, irritability and automaticity make possible the beneficial influences of mephentermine upon cardiac action. The alterations in properties will explain the efficiency of mephentermine in the prevention of arrhythmias during cyclopropane anesthesia, its use to benefit or terminate atrial flutter due to a circus movement, its ability to stop a pulsus alternans or an arrhythmia due to topical application of aconitine to the atrium or to reverse the prolonged P-R interval of digitalis intoxication. The test animal in these experiments was the dog. A number of clinical applications of this drug will be shown.

(Booth 23)

Clinical and Experimental Observations on Angina Pectoris. *Myron Prinzmetal, Rexford Kennamer, Takashi Wada, and Naci Bor, Los Angeles, Calif.*

The exhibit consists primarily of observations on angina pectoris, including a previously undelineated form. Twenty-six cases of this type have been observed (unpublished material). The exhibit will also describe a new EKG pattern of infarction, the use of adrenal steroids for complete heart block, etc.

(Booths 55 and 56)

Rehabilitating the Coronary Patient. *Shepard Shapiro, New York, N. Y.*

Approach to the long-term management of the patient with coronary arteriosclerosis which recognizes that primary concern must be given to the patient's adjustment to his environment. Avenues of psychologic rehabilitation are explained and evaluated. Results of an extended follow-up of more than 100 patients are cited.

(Booth 15)

Permanent Aortic Intubation in Rats. *Joseph T. Still, Washington, D. C.*

Surgical technic of intubation in pictorial form. Also potential and already established uses of this procedure.

(Booth 5)

Treatment of Quinidine and Procaine Amide Intoxication. *Fred Wasserman, Leonard Brodsky, Morris M. Dick, John H. Kathe, and Paul L. Rodenski, Coral Gables, Fla.*

The exhibit consists of 3 panels: they depict experimental observations on quinidine and procaine amide intoxication and show the clinical application in the successful treatment of 2 representative patients with quinidine and procaine amide, respectively.

(Booth 12)

Working Together to Keep Hearts Strong, 1948-1958 *American Heart Association, New York, N. Y., and National Heart Institute, Bethesda, Md.*

This exhibit was designed for the Third World Congress of Cardiology, to commemorate ten years of cooperation between the American Heart Association and the National Heart Institute. It consists of displays illustrating the complementary efforts of the two agencies in support of cardiovascular research, professional and public education and community service. A display of teaching aids is part of the exhibit.

(Booths 28 and 87)

TECHNICAL EXHIBITS

All Exhibits Will be Displayed in the Civic Auditorium

Armour Laboratories, Division of Armour & Company, Kankakee, Ill. (Booth 80) *will feature Arcofac, a widely accepted cholesterol-lowering product on the market today. Their representatives will be happy to discuss products of their manufacture with all who wish to visit the booth.*

Bowen & Company, Inc., Bethesda, Md. (Booth 82). *New developments in the use of their accurately calibrated Ballistocardiograph, Smith-Perls Model. They will display Welsch Self-Retaining Electrodes, standard and infant sizes. QT Calculator for determining the QTc or the QT Ratio, Liquid Dispenser for use with alcohol and other cleansing liquids, and Krasno-Graybiel Metal Plastrodes, requiring no electrode paste.*

Burdick Corporation, Milton, Wis. (Booth 75) *will exhibit their modern line of electrocardiographic equipment. A feature of especial interest will be their new EK-3 duel-speed model. Representatives of the factory sales and engineering departments will be on hand to explain the features of this new equipment.*

Burroughs Wellcome & Company (USA) Inc., Tuckahoe, N. Y. (Booth 71). *The extensive research facilities of their company, both here and in other countries, are directed to the development of improved therapeutic agents and technics. Through such research they have made notable advances relating to leukemia, malaria, diabetes and diseases of the autonomic nervous system, and to antibiotic, muscle-relaxant, antihistaminic, and antinauseant drugs. An informed staff at the booth will welcome the opportunity to discuss their products and latest developments with you.*

Burton, Parsons & Company, Washington, D. C. (Booth 53) *invite you to their booth, where information and samples will be available for their EKG Sol, the modern electrode cream for electrocardiography and electroencephalography, along with their original bulk preparations, Konsyl and L. A. Formula. L. A. Formula contains 50 per cent bulk producing material dispersed in an equal amount of lactose and dextrose. Konsyl, on the other hand, contains 100 per cent bulk producing material and is recommended for the obese, the diabetic, and others with restricted caloric diets.*

Cambridge Instrument Company, Inc., New York, N. Y. (Booths 49 and 50). *Their new "Versa-Scribe," the Versatile Portable Electrocardiograph; their "Simpli-Scribe" Model Direct-Writing Portable Electrocardiograph and their Standard String Galvanometer Type Electrocardiograph will be displayed. Also other important instruments, including the Audio-Visual Heart Sound Recorder, Operating Room Cardioscope, Educational Cardioscope, Multi-Channel Physiological Recorder, Electrokymograph, Plethysmograph, pH Meters, and Pulmonary Function Tester. Their engineers will be glad to give you complete information on these instruments.*

Carnation Company, Los Angeles, Calif. (Booth 51) *welcomes friends of long standing, as well as new members, of the American Heart Association. A refreshing drink of their Instant Nonfat Milk will be served. Their representatives will be pleased to discuss the physician-researched material for use in your practice as a service of their company.*

CIBA Pharmaceutical Products, Inc., Summit, N. J. (Booth 76) *will feature the original, pure crystalline alkaloid of Rauwolfia. Serpasil has been found extremely useful as a tranquilizer in treating patients whose adjustment to life is complicated by anxiety, irritability and various psychoses. Patients feel calm, yet in properly adjusted doses retain their drive and energy. It is highly effective in many conditions where barbiturates have been commonly prescribed.*

Coca-Cola Company, Atlanta, Ga. (Special Area). *Ice-cold Coca-Cola will be served through the courtesy and cooperation of the Coca-Cola Company.*

Colson Corporation, Elyria, Ohio (Booth 56). *On display will be Colson's new infra-red Densitometer for use with Fox Green. A new linear instantaneous cardiotachometer, based on a new principle and displaying pulse rate directly in numerical form, will be demonstrated. Pulse information can be picked up from the subject by earpiece, fingertip pick-up, blood pressure cuff, or ECG with standard attachments offered. A new low resistance spirometer will be on display, suitable for measurement of maximum breathing capacity and other pulmonary functions. Results are immediately displayed in*

numerical form. Colson's Model 110 Automatic Blood Pressure Recorder will be demonstrated with a new attachment, which permits measurement of systolic or diastolic pressure approximately every 3 to 4 seconds. Rapid changes, such as in the Valsalva maneuver, can be followed without arterial puncture.

Corco Incorporated, Culver City, Calif. (Booth 31). *A completely autoclavable stationary screen heart-lung, designed and developed for the University of Southern California Medical School. This one-chambered oxygenator introduces an automatic filmer and a fool-proof distribution chamber. Only one man is required to operate the apparatus.*

Darwin Laboratories, Los Angeles, Calif. (Booth 43). *LH 400: (Lipo-Hepin) Sodium Heparin USP —400 mg./cc. This new product is ideal for both long-term and short-term anticoagulant therapy. Lipoprotein lipase (fat clearing) action is accentuated. Patient self administration is greatly simplified and entirely feasible. Clotting times, using full anticoagulant dosages, are not required in either the ambulatory or hospitalized patient using LH 400 technics. Dar-Zyme: A purified trypsin, antibiotic salve for topical use whenever enhancement of healing or debridement of nectrotic tissue is desired. Wounds are rapidly deodorized and healthy granulation tissue is formed promptly. Adrenalex-Geriatric: A balanced hormone, vitamin and hematopoietic combination to assure adequate endocrine activity.*

Davies, Rose & Company, Ltd., Boston, Mass. (Booth 33). *A cordial invitation is extended to the members to visit their booth. Although most physicians need no introduction to their outstanding cardiac therapies—Pil. Digitalis and Tablets Quinidine Sulfate (Natural), their representatives, Messrs. H. V. Orne and G. F. Day, will be on hand to explain the dependability of their laboratory productions.*

Electronics for Medicine, Inc., White Plains, N. Y. (Booth 79). *A new 8-channel Research Recorder provides both scalar and loop tracings with an improved cathode ray camera. Cardiovascular and respiratory pressures, ECG, EEG, phonocardiograms and oxygen saturation can be recorded along with polarographic measurements, integrals, derivatives, and pressure gradients. The Cardiology Teaching Aid permits simultaneous tape recording for phonocardiogram and ECG or pulse wave, with visual and aural examination and permanent tracings.*

Encyclopaedia Britannica, Chicago, Ill. (Booth 9) *announces the release of a New Edition. Thirteen years of intensive editorial effort and considerable investment are reflected in this New Edition. You are cordially invited to inspect in their booth the finest* Britannica *ever published.*

Endo Laboratories, Richmond Hill, N. Y. (Booth 5) *will present Coumadin (warfarin) sodium, an advance in anticoagulant therapy. The subject of continuing flow of clinical reports relating to its usefulness in the treatment of coronary occlusion with myocardial infarction and for the treatment and prophylaxis of thrombotic and thrombo-embolic disorders, Coumadin possesses a number of desirable features. Among these are: early onset and predictability of anticoagulant effect; infrequent "escapes" from therapeutic control; no known systemic toxicity; readily reversible action with vitamin K_1; effectiveness for initial and long-term anticoagulation; and availability in both oral and parenteral forms.*

C. B. Fleet Company, Inc., Lynchburg, Va. (Booth 36) *will exhibit Clysmathane, its most recent contribution in the field of medication by rectum—an advanced method of xanthine therapy. Clysmathane is a stable solution of theophylline monoethanolamine, easily retained, rapid and uniform absorption, prompt and predictable blood levels, and with no rectal irritation after prolonged use.*

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Yonkers, N. Y. (Booth 77) *will feature Preludin, nonamphetamine appetite suppressant and Sintrom, potent oral anticoagulant with intermediate duration of action. Also on display will be Butazolidin and Butazolidin-Alka, potent nonhormonal antiarthritic and anti-inflammatory agent also effective in the treatment of superficial thrombophlebitis; Medomin, the hypnotic which provides "natural" sleep; and sterosan-Hydrocortisone cream and ointment for comprehensive control of a wider range of dermatoses.*

General Foods Corporation, White Plains, N. Y. (Booths 57 and 60) *invites you to stop by their booth for a cup of Instant Sanka, a heart's coffee. Sanka is pure coffee, 97 per cent caffein-free. Do try Instant Sanka, and while at their booth, register for professional samples and leaflets.*

Grass Instrument Company, Quincy, Mass. (Booth 26) *will exhibit the Direct Recording Polygraph Model 5. This versatile instrument is designed*

to measure neurologic and circulatory functions, including EEG, EKG, EMG, respirations, pressure, plethysmography O_2, CO_2, PGR. The application is in the operating room, clinic, laboratory and class room.

Lane & Stratton, Inc., Medical Publishers, New York, N. Y. (Booths 72 and 73). *Mr. Frank Kurzer welcomes you to their booths where you may examine such new books as: the new quarterly publication,* Progress in Cardiovascular Diseases, *edited by C. K. Friedberg, M.D.; Kossmann's* Advances in Electrocardiography; *Scherf and Boyd's* Cardiovascular Diseases, *3rd Revised Edition; Osserman's* Myasthenia Gravis; *Wright and Millikan's* Cerebral Vascular Diseases; *Luisada and Liu's* Intracardiac Phenomena; *Bjerkelund's* The Effect of Long Term Treatment with Dicoumarol in Myocardial Infarction; *Hoobler's* Basic Mechanisms of Arterial Hypertension; *and many other books essential for your daily practice.*

Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, N. Y. (Booth 74). *Their books of great interest and value will include* Bayley's Biophysical Principles of Electrocardiography, *Rosenbaum and Belknap's* Work and the Heart, *and Hoobler's* Hypertensive Disease. *You will also find at their booth Plotz's* Coronary Heart Disease, *Gardberg's* Clinical Electrocardiography, *Abramson's* Peripheral Vascular Disorders, *and all their other books now in print. You are cordially invited to browse at leisure.*

Lea & Febiger, Philadelphia, Pa. (Booth 40) *invites you to examine such books as Katz and Pick's* Clinical Electrocardiography; *Master, Moser and Jaffe's* Cardiac Emergencies and Heart Failure; *Goldberger's* Heart Disease; *Goldberger's* Unipolar Lead Electrocardiography and Vectorcardiography; *Burch and Winsor's* Primer of Electrocardiography; *Burch's* Primer of Cardiology; *Burch, Abildskov and Cronvich's* Spatial Vectorcardiography; *and books in related fields.*

Eli Lilly & Company, Indianapolis, Ind. (Booths 69 and 70) *cordially invite you to visit their exhibit. Their sales people in attendance welcome your questions about their products and recent therapeutic developments.*

Macmillan Company, New York, N. Y. (Booth 39) *will feature the new* Electrocardiogram Clinics *by Riseman and Sagall. The recent publications,* Heart Disease in Infancy and Childhood *by Keith-Rowe-Blad, and* Cardio-Charting *by Brisbier, will also be shown along with many other books of particular interest to cardiologists.*

Mark Company, Randolph, Mass. (Booth 64). *Latest mechanical heart-lung apparatus, including membrane, disc, screen and bubble diffusion oxygenators will be exhibited, as well as many essential accessories. In addition to this they will exhibit the Schwarzer multichannel recorders, heart and lung models for teaching purposes, Mayo Clinic cardiovascular cannula, flow meters, oxygen electrodes, etc.*

Merck Sharp & Dohme, Division of Merck & Company, Inc., Philadelphia, Pa. (Booths 37 and 38). *A new and very promising diuretic is featured. Since the principal action of "Diuril" is a marked enhancement of the excretion of sodium, chloride and water, it has been designated as a saluretic agent. This new compound achieves a profound electrolyte and water diuresis, without attendant toxic effects and other disadvantages peculiar to the mercurials and certain other diuretic agents. Technically trained personnel will be present to discuss this and other subjects of clinical interest.*

North American Philips Company, Inc., New York, N. Y. (Booths 46, 47 and 48). *Heart catheterization with angiocardiographic possibilities, using the Philips Image Intensifier with closed-circuit television and 16 and 35 mm. cine cameras. Image Intensifier reduces radiation hazards to an absolute minimum and increases fluoroscopic and angiographic information tremendously. Cine films give complete physiologic process and thus enhance diagnosis.*

Picker X-ray Corporation, White Plains, N. Y. (Booths 85 and 86). *They will show the first commercially available x-ray table specifically designed for the cardiologist-radiologist team. This new unit facilitates angiography, cardiac catheterization and cineradiography. It includes: (1) their new 8" Image Intensifier, (2) TV (single or multiple monitors), optical viewing, and (3) synchronized cineradiography at 60 frames per second.*

J. B. Roerig and Company, New York, N. Y. (Booth 81), *will feature Cartrax, a combination of Petn plus Atarax, linked together to provide freedom from pain and tension in angina pectoris. Petn is the most effective drug currently available for prolonged prophylactic treatment of angina pectoris, while Atarax provides safe and effective tranquilization against the attendant fear. Literature and samples are available to physicians at the booth which you and your friends are cordially invited to attend.*

Sanborn Company, Waltham, Mass. (Booths 41 and 42). *Research worker and clinician alike will find much of interest to examine and discuss at their booth: recording systems (single-channel and*

multichannel, direct, photographic, and tape), monitoring, oscilloscopes and transducers (pressure, temperature, etc.). Much of this equipment will be demonstrated by working displays, or by preproduction models, to aid understanding of function and of operating features. Their competent representatives from the engineering, technical and sales divisions will be at hand to show the instruments and to discuss your recording problems without obligation.

Sandoz Pharmaceuticals, Hanover, N. J. (Booth 67) *cordially invite you to visit their display of Cedilanid pure glycoside (lanatoside C) of digitalis lanata with quick onset of action, quick excretion, low toxicity useful for i.v. administration in cardiac emergencies. Acylanid has all the advantages of digitoxin but the safety of whole leaf digitalis. Any of their representatives in attendance will gladly answer questions about these and their other products.*

Schieffelin & Company, New York, N. Y. (Booth 29) *will exhibit C.R.P.A. (C-reactive Protein Antiserum), a unique diagnostic aid for the detection of inflammatory diseases. This practical and simple test brings your patient's hidden inflammation to light. Unlike the E.S.R., there is no normal range. It is either negative or positive. The quantity of the precipitate reflects the severity of the condition. The precipitate diminishes as therapy reduces inflammation. Danilone, the oral anticoagulant of choice, has been found to possess decided clinical advantages over other anticoagulants in the therapy and prophylaxis of thrombo-embolic diseases. Representatives will be on hand to discuss this with you.*

G. D. Searle & Company, Chicago, Ill. (Booth 65) *cordially invite you to visit their booth, where their representatives will be happy to answer any questions regarding their products of research. Featured will be Enovid, the new synthetic steroid for treatment of various menstrual disorders, Zanchol, a new biliary abstergent, Nilevar, the new anabolic agent, and Rolicton, a new safe, nonmercurial oral diuretic. They will also feature Vallestril, the new synthetic estrogen with extremely low incidence of side reactions; Pro-Banthine, the standard in anticholinergic therapy; and Dramamine, for the prevention and treatment of motion sickness and other nauseas.*

E. R. Squibb & Sons, New York, N. Y. (Booth 25), *have long been leaders in the development of new therapeutic agents for prevention and treatment of disease. The results of their diligent research are available to the medical profession in new products or improvements in products already marketed. This year they will feature Randixin, Squibb Whole Root Serpentina, the basic, all-purpose hypotensive agent. They will be pleased to present up-to-date information on these advances for your consideration.*

Statham Instruments, Inc., Los Angeles, Calif. (Booth 44). *Four types of their unbonded strain gage manometers intended especially for biologic measurements will be displayed by experienced engineering personnel. These 4 models of their pressure transducers have found wide acceptance in the field of cardiac catheterization because of their inherent stability, excellent dynamic response, and simplicity of operation.*

United States Catheter & Instrument Corporation, Glen Falls, N. Y. (Booth 78). *Specialists in the manufacture of cardiac catheters, electrodes and tubings. Introducing a complete line of woven and knitted Teflon arterial grafts. Research engineers, well versed in design and production of cardiac catheters, will discuss problems, ideas, new developments, etc. at their booth.*

Varick Pharmacal Company, Inc., Hicksville, N. Y. (Booth 61). *In a clinical comparison with 5 other commonly used glycosides, Digitaline Nativelle is exceeded only by ouabain in rapidity of improvement, is rarely toxic and is recommended in cases with a low threshold of toxicity. In all forms—tablet, intramuscular, intravenous, oral solution—identical dosage, identical effect.*

Walker Laboratories, Inc., Mt. Vernon, N. Y. (Booth 35). *Hedulin (PID) the oral anticoagulant of choice. Hedulin is their brand of Phenindione (not a coumarin derivative), 2-Phenyl-1, 3-indandione (PID), a new, substantially safe, oral anticoagulant. Extensive clinical experience with Hedulin has shown it to be preferable to all other anticoagulants in the prophylaxis and treatment of thromboembolic disorders of all types. Full details pertaining to the drug, and reprints of all medical papers, are available in complete portfolio form.*

Wallace Laboratories, New Brunswick, N. J. (Booth 32) *look forward to discussing Miltrate, a new treatment for angina, with you. The drug consists of 200 mg. of Miltown, plus 10 mg. of Peiin, providing a new dovetailed therapy preventing both cause and fear of angina. Miltrate has been proved safe for long-term use.*

Warner-Chilcott Laboratories, Morris Plains, N. J. (Booth 52). *A visit to their booth will be well worth while, especially in the interests of your cardiovascular patients and those with mental or emotional disturbance. They will feature 2*

nically tested and proven agents: Peritrate—*aid you in the management of patients with gina pectoris; and* Pacatal—*a profound atar- tic agent with a "normalizing" action.*

Wa rs Corporation, Rochester, Minn. (Booth 84). *atured will be the new XC-100A densitometer r dye curve recording in cardiac research and gnosis using the Fox Green dye. Also oxim- rs, photographic recorders, nitrogen gas alyzer, cardiotachometer and thermistor with trasensitive, fast probes.*

Wi throp Laboratories, New York, N. Y. (Booth 83). *Filcoron, a new "flavor-timed," dual action, coro- ary vasodilator for angina pectoris; orally for pendable prophylaxis and sublingually for im- ediate relief. The sublingual-oral tablet has quick layer of nitroglycerin 0.4 mg. over a entral core of prolonged acting pentaerythritol tetranitrate 15 mg.*

Wyeth Laboratories, Philadelphia, Pa. (Booth 45) *will feature Bicillin.® Injection (benzathine penicillin G) long-acting penicillin ideally suited for prophylactic and therapeutic use. Offers simplified protection against recurrent attacks of rheumatic fever with a single injection per month. Equalysen® (meprobamate and pentolinium tartrate) offers effective lowering of blood pressure and symptomatic relief for patients with essential hypertension. Thiomerin® (mercaptomerin sodium) Injection and Rectal Suppositories, useful in control of edema in congestive heart failure. Virtually free of local or systemic toxicity. Injection Wyamine® Sulfate (mephentermine sulfate) useful in the prophylaxis and management of hypotensive states not associated with hemorrhage. Elicits an immediate rise in blood pressure with no adverse effect on the myocardium, central nervous system or heart rate.*

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